1.0 INTRODUCTION

Practitioners of lay medicine still use herbs in lone localities, where scientifically trained medical staff is not readily available, or where the latter have lost the confidence of the patients. The lay medical practitioners rely on experience handed down through the generations and on common sense. Although such persons may cause a few medical accidents, which might also happen to medical doctors, especially of past generations, in some cases, the lay treatment can be effective and, therefore, deserves an examination with the methods of modern science. The flavonoids, polyphenols, terpenoids appear to have played a major role in the successful medical treatments of ancient times, and their use has been persevered up to now. The recent interest in the properties of these phytochemicals has several converging explanations

1.1 GYMNEME SYLVESTRE – DESCRIPTION

Plants have always been a prototypical source of drugs and many of the formerly available drugs have been derived directly or indirectly from them. A wide array of plant derived active principles representing numerous chemical compounds has demonstrated activity consistent with their possible use in the treatment of several diseases [1]. In recent years, the use of ethno-botanical information in medicinal plant research has gained considerable attention in segments of the scientific community [2]. In one of the ethno-botanical survey of medicinal plants commonly used by Kanitribals in Tirunelveli hills of Western Ghats in Tamil Nadu, India, has revealed that *Gymneme sylvestre* as the most
important species according to their use [2]. The use of plant parts and isolated phytochemicals for the prevention and treatment of various health ailments has been in practice from time immemorial [3].

One of such plants is *Gymnema sylvestre* R. Br., commonly known as 'Meshasringi' which is distributed over most of India and it has a reputation in traditional medicine as a stomachic, a diuretic and as a remedy to control diabetes mellitus. *Gymnema sylvestre* R. Br [4] is a woody, climbing plant that grows in the tropical forests of central and southern India and other parts of Asia [5]. It is a pubescent shrub with young stems and branches, and has a distichous phyllotactic opposite arrangement pattern, which are 2.5-6 cm long and are usually ovate or elliptical, the flowers are small, yellow, in umbellate cymes and follicles are terete, lanceolate, up to 3 inches in length [6].

*Gymnema sylvestre* has been used in the treatment of diabetes since ages in folk, ayurvedic and homeopathic systems of medicine [1, 4, 7]. It is also used in the treatment of asthma, eye complaints, family planning, snakebite, urinary complaints, stomach ailments, piles, chronic cough, breathing troubles, colic pain, cardiopathy, constipation, dyspepsia, hemorrhoids and hepatosplenomegaly [8]. In addition, it also possesses antimicrobial [9], antitumor [5], anti-obesity [10], anti-inflammatory [11], and anti-hyperglycemic activity [12].

Its flowers, leaves, and fruits contains alkaloids, flavones, saponins, sapogenins, anthraquinones, hentriacontane, pentatriacontane, α and β-chlorophylls, phytin, resins, d-quercitol, tartaric acid, formic acid, butyric acid, lupeol, β-amyrin related glycosides and stigmasterol having main principle bioactive compounds viz. gymnemic acids, gymnemasides, gymnemagenin, gurmarin, gymnemosides, gymnemanol, gymnemasins, gypenoside, and conduritol which act as therapeutic agent and play vital role in many therapeutic applications. The commercial exploitation of this plant and their secondary metabolites are some of the major prospective of this rare medicinal herb. The focus of the present review is to achieve the potential of therapeutic value of this herb and mechanism and action of their secondary metabolites [13]. Medicinal plants have been
subjects of man’s curiosity since time immemorial. Almost every civilization has a history of medicinal plant use [14].

Approximately 80% of the developing countries in the world depend on the traditional medicine for their primary health care among which 85% involves herbal extracts [15]. Usage of phyto medicine has increased in the last few decades and almost more than 500 plant species collected from the wild are used for their ingredients. Plants play a crucial role in the application of therapeutic drugs from the higher plants and it continues to occupy all important niches in modern medicine. Most of the compounds used in today’s modern medicine have a complex structure, and synthesizing these bioactive compounds chemically at a low price is not feasible [16].

The disillusionment of consumers over modern health has led them to seek alternatives in traditional medicine. But lack of legislation or effective agreements on conservation of biodiversity has resulted in ‘slaughter harvesting’ of medicinal plants and massive depletion of biodiversity. The increased demand for herbal medicine had renewed interest by multinational pharmaceutical industry in bio-prospecting. The increasing awareness about the drugs side effect had made the western pharmaceutical industries to turn towards plant based Indian and Chinese medicine.

The resurgence of public interest in plant based medicine coupled with rapid expansion of pharmaceutical industries has necessitated an increased demand for medicinal plants. Plants are a tremendous source for the discovery of new products of medicinal value for drug development. Several distinct chemicals derived from plants are important drugs currently used in many countries. Many drugs sold today are simple synthetic modifications or copies of naturally obtained substances. The evolving commercial importance of secondary metabolites has in recent years resulted in a great interest in the secondary metabolism, particularly in the possibility of altering the production of secondary metabolites [17]. Different strategies such as in vitro system have been extensively studies to improve the production of plant chemicals.
In recent years, traditional system of medicine has become a topic of global importance. Although modern medicine may be available in developed countries, herbal medicine (phyto pharmaceuticals) have maintained popularity for historical and cultural reasons. Many of these plant species that provide medicinal herbs have been scientifically evaluated for their possible medical applications. It has been mentioned that natural habitats for medicinal plants are disappearing fast together with environmental and geopolitical instabilities, due to which acquiring of plant derived compounds are increasingly difficult.

1.2 ANTIULCER ACTIVITIES OF MEDICINAL PLANTS

Plants with medicinal properties “The gift of mother, nature of mankind” are in use for centuries in the traditional system of medicine like Ayurveda, Unani, Siddha etc., in India and other countries for the treatment of diseases including ulcer. They are considered to be effective and nontoxic [18]. Peptic ulcer disease (PUD) was recognized through ages and civilization. In fact, gastrointestinal disease has attracted so much attention from patients and clinicians as that of peptic ulcer [19]. Dyspepsia in its variable form has been mankind’s companion ever since the advent of bad cooking, over indulgence and anxiety. Since one “is not altogether fit for the battle of life who is in perpetual contention with his dinner”, considerable energy has gone into relieving the symptoms of gastric upset and peptic ulcer disease [20].

Peptic ulcer may also be defined as pathological lesions such as ulcers of any portion of the gastrointestinal tract exposed to acid activated pepsin. It is generally acknowledged that an ulcer results from an imbalance between aggressive gastric factors and resistance factors. The term “peptic ulcer” is used to refer a group of ulcerative disorders of the upper gastrointestinal tract which appears to have common role to play in the participation of gastrointestinal tract which appears to have common role to play in the participation of acid-pepsin in their pathogenesis [21]. The causative factors of PUD are many and important among them are hyperacidity, stress, NSAID’s, mucosal barriers and food habits. Recent information suggest that the prevalence and changing pattern of
the disease, is mainly due to a bacterial organism, *Helicobacter pylori* which colonies the gastric mucosa, particularly the anural region. *H. pylori* are often reported in about 100% of patients with gastric ulcers [21].

Until recently the pathogenesis of duodenal ulceration has been attributed to an in balance between aggressive factors such as acid and pepsin that damage the gastric mucosa and protective factors such as prostaglandin’s that prevents the damage. Recent evidence relates *H. pylori* to the pathogenesis of chronic duodenal ulcer, as *H. pylori* infection and anural gastritis are found together in more than 95% of patients with duodenal ulcers. Thus *H. pylori* infection is now strongly associated with chronic duodenal ulceration [22]. Duodenal ulcer is twice as common and benign gastric ulcer is four times more common in men than in women. Marshall and Warren [23] were the first to describe the association of the presence of campylobacter like organism in the central mucosa with histological evidence of antral gastritis as well as peptic ulcer, especially duodenal ulcers. Autoimmune phenomena are absent in type gastritis and it has been contributed as idiopathic. There is now evidence that the gram negative bacterium *H. pylori* may be important in the etiology of type gastritis [24].

Treatment of PUD in modern medicine has undergone remarkable degree of transformation. The therapeutic management of PUD includes antacids, anti-cholinergic and antispasmodic drugs, H2 receptor antagonists such as cimetidine, ranitidine, farmotidine and proton pump inhibitors viz. Omeprozole, Lansprazole, Patoprazole etc. In the recent past, with the acknowledgement of the etiological association of *H. pylori* in PUD, a range of anti-bacterial such as Metronidazole, Tiddazole, Ampicillin, Amoxycillin, Clarithromycycin, Tetracycline, etc., are being used in a combined regimen to provide both bacteriological and histological remedy [22].

Plant extracts are some of the most attractive sources of new drugs and have been shown to produce promising results for the treatment of gastric ulcer [25]. During the past 40 years, the frequency of duodenal ulcer now appears to be approximately as common in males as in females [26].
1.3 ROLE OF PLANTS IN THE TREATMENT OF AILMENTS

Data from 1991, indicates that more than half of the world’s 25 best-selling pharmaceuticals are either themselves natural products or derived from natural products [27]. Within the developed countries, 25% of medicines contain active principle derived from plants, and the majority of drugs in current use were developed following studies of traditional herbal treatments. Aspirin, Quinine, Theophiline, Pencillin G, Morphine, Palcitaxel, Digoxin, Vincristine, Doxorubicin, Cyclosporin and Vitamin A all share two important characteristics: They are in the cornerstones of modern pharmaceutical care and they are all natural products. So natural products, so called secondary metabolites from plants continue to be an important segment of modern drugs in clinical use in spite of all substantial advances that have been made in synthetic drug-design chemistry. There is still a great thirst for novel compounds with unique mechanisms of action in the field of Medicine. The medications used in PUD management include acid suppressants (antacids, histamine-2 receptor blockers, and proton pump inhibitors) and gastric mucosal protectants, for relief of symptoms and to promote ulcer healing, and antibiotics to eradicate *H. pylori* when it is present. All are found to produce side effects such as constipation, diarrhea and toxic effects on chronic administration.

However, comparative pharmacological and Biochemical studies on leaves of variants of *Gymnema sylvestre* was not carried out. It is essential to standardize traditional medicine and to know their therapeutic potential. Even though, medicinal plants are used increasingly throughout the world in healthcare, scientific validation and standardization of herbs and herbal drugs need to be carried out for most of the medicinal plants used in traditional systems of medicine. Therapeutic potentials of medicinal plants depend upon the quality and quantity of biological active compounds they possess. Medicinal plants show variation in their biological compounds due to various factors like season, growth stage, climate, and soil type and genetic. There are varieties of variants within a single species of medicinal plant which tend to show difference in the quality and quantity of biological active compounds.
1.4 RADIOPROTECTION

Due to the exposure of cells to low linear energy transfer (LET), radiation leads to increased generation of reactive oxygen species, which shifts the balance between pro-oxidants and antioxidants in cells, the former resulting in severe oxidative stress and ultimately cell death [28]. An agent that can modulate the balance or shift the balance toward antioxidant can be of immense help to cellular systems in dealing with oxidative stress and in augmenting recovery [29]. Several molecular drugs of synthetic and natural origin are being tried in various experimental models to mitigate radiation injury [30]. Among different molecular radio protectors, WR-2721 and related compounds have been found to be most promising, but the side effects associated with them have restrained their use. In view of this, the search for newer and more effective agents is inevitable.

India has a rich heritage of medicinal plants, many of which have long been explored for their various bioactivities, but the radio protective potential of the plants has barely been explored. Some of these plants have already been reported to possess strong antioxidant activity [31]. In this context, Gymnema sylvestre R. Br. (Asclepiadaceae), a slow growing, perennial climber found in central and peninsular India [32] has been evaluated for its radio protective efficacy. It is commonly called “mesasrngi” or “Gurmar,” meaning “sugar destroying,” which is suggestive of the anti-sweet quality experienced when, after chewing one or two leaves, one is unable to detect a sweet taste. According to the Ayurvedic Pharmacopoeia of India [33] both the dried leaf and root of Gymnema, depending on dosage, form, and formulation, are also used in the treatment of svasa (bronchial asthma), kasa (cough), kustha (leprosy and other skin diseases), and vrana (wounds), among other conditions. The leaves of the plant are also used as a digestive, antiviral, diuretic, anti-allergic, hypolipidemic, and anti-obesity agent. Decoctions of the leaves of this plant are taken orally for the treatment of diabetes [34] or are heated with sesame oil to form emulsions, which may be used in drops to treat eye diseases [35].
The plant contains gurmarin [36], conduritol A, gymnema saponins [37], gymnemasins [38], gymnemosides [39], stigmasterol, lupeol, quercitol, glycosides of kaempferol, and quercetin [40]. Gymnemic acid, a mixture of at least 17 different saponins, is the main constituent of Gymnema [41]. The radio protective efficacy of this plant is still not well evaluated, particularly with reference to the different organs. The living tissues are considered to be sensitive to oxidative damage because of the high content of easily oxidizable polyunsaturated fatty acids and the highest rate of aerobic glycolysis of all tissues. The tissues consume 20% of body oxygen and glucose, and for this reason it is sensitive to hypoxia [42].

On the other hand, the living system has a relatively weak antioxidant defense system due to low levels of superoxide dismutase, catalase, and glutathione peroxidase [43]. A growing body of evidence indicates that various pathological conditions, including cardiovascular disease, arthritis, various cancers, and Alzheimer’s disease, are associated, at least in part, with the damaging effects of uncontrolled free radical production [44]. External supplementation with antioxidants is recommended to protect cells from the deleterious effects of such oxidative stress conditions. Ample research indicates that age-related neuronal behavioral decrements are the result of oxidative stress that may be ameliorated by antioxidant’s [45].

We have studied the mitigation of the deleterious effects of ionizing radiation in fresh water fish using the leafy extracts of Gymnema sylvestre extract (GSE), with special reference to gills, liver and muscle tissue. The free radical–scavenging activity of GSE was investigated by employing various techniques like micronucleus, comet assay and antioxidant enzymes like catalase, SOD to demonstrate the radio-protective activity of Gymnemic acid–rich Gymnema sylvestre extract of the leaves.

G. sylvestre is used in several commercial formulations viz. Madhu Rakshak, Nature care Gymnema (Dabur India Ltd., New Delhi, India), Dolabi (Hamdard Laboratories, New Delhi, India), blood sugar (Nutrasanus), glucose Support (Vitabse, Monroe), Nutrilite (Amway Pvt. Ltd.) Dibecon, Ayurslim, Meshashringi (Himalaya Drug
Co., Bangalore, India) and many others [46, 47]. Since some researchers reported the seasonal variation of bioactive gymnemagenin’ in *Gymnema sylvestre* [46, 48], so it is indispensable to characterize the phytochemical constituents of the collected plant for our study. So initially we have characterized the phytochemical constituents of the leaf extract and characterized for the pharmacological properties. Even though many commercial drugs have included *G. sylvestre* as one of the component there are still date no reports are available on the anti-stress, anti-allergic, and antiulcer activity of the plants extracts; so the present study was performed using various in vivo systems to explore the underlying mechanisms and mode of action for these activities.

Hence, the present work was undertaken with a view to compare phytochemical, biochemical and pharmacological profiles of leaves, that are commonly available in and around Thanjavur and hence *Gymnema sylvestre* grown in different locations were selected for the present study to determine the variation in the phytochemical profile of this plant. Along with the preliminary phytochemical analysis of leaf extracts, quantitative phytochemical screening of leaf extracts, HPTLC and GC-MS profiles were done and compared with the standard compound. Biochemical and Pharmacological evaluation of methonolic extract from the leaves of *Gymnema sylvestre* were studied for its Anti-ulcer, Anti-inflammatory, Anti stress, Anti-oxidant, and Anti-microbial activities. The extracts were also evaluated for its anti genotoxic and radioprotective profiles in fresh water fish model.

The purpose of our study was also to identify the natural bioactive compounds present in the leaf extracts of *Gymnema sylvestre* possessing radio protective properties. Since reports are available that the flavonoids, saponin, triterpenes present the plant leaves have protective properties against radiation induced damages. The major bioactive component present in *Gymnema sylvestre* such as gymnemic acid and gymnemagenin which belong to triterpene saponin, were tested for its radioprotective effects against 60Co irradiation induced in fish model using the fresh water fish *Pangasius sutchi*. According to the current radioprotection research the antioxidative effects of the compounds were done in fish by quantifying the antioxidant enzymes involved in the ROS and the
occurrences of nuclear damage by micronucleus assay and alkaline comet assay. The results can offer some cytogenetic and physiological information that can be used in further research on animal and human cells.