International Journal of Advance Research in Science and Engineering
Volume No.07, Special Issue No.04, March 2018
www.ijarse.com
IJARSE
ISSN: 2319-8354

Achillea millefolium L.: A Promising Health Aid In Modern Pharmacology.

Misbah Majid[1]* , Mudasir Roshan[1] ** ,
Lubna Andleeb[1] , Mohmad Ishaq Bhat[1]

[1]*Department of Botany, Govt. Degree College, Ganderbal*

***Presenting author** : Misbah Majid*

****Corresponding author:** Mudasir Roshan*

ABSTRACT

Plants and plant products have historically been incredible as a source of therapeutic agents. In the current scenario, ethnopharmacological approaches to the medicinal herbs are being made in attempts to search for novel drugs with new and different mechanism of action. Achillea millefolium L. known as 'yarrow' finds its use in traditional medicinal system of several cultures worldwide as antibacterial, anti-inflammatory, anti-edemic, vermifuge, analgesic and expectorant etc. in herbal therapy. The presence of several bioactive compounds which have been so far discovered from this magical herb have confirmed its folklore utilization making it a promising candidate for future drug development.. However, the tremendous benefits derived from indigenous knowledge of this medicinal herb go largely uncredited. The present review summarizes a detailed ethnopharmacological and pharmacognostic study on Achillea millefolium L. reported to date, that could provide a promising sign in the resurgence of the traditional usefulness of this medicinal herb and increases the probability of finding new lead compounds which could act as phytomedicines and, in the long run, prove beneficial for further development of modern drug industry.

Keywords: Achillea Millefolium L., Ethnopharmacology, Folklore, Pharmacognostic, Phytomedicine.

1. Introduction

Achillea millefolium L., (Kingdom: Plantae, Phylum: Tracheophyta, Class: Magnoliopsida, Order: Asterales, Family: Asteraceae, Genus: *Achillea*, Species: *A. millefolium L.)*, native to Northern Hemisphere in Asia, Europe, and North America [1] and is commonly known as 'Yarrow' or 'Milfoil' or 'Thousand leaf' (referring to many segments of its foliage) in English and 'pahelkutch', 'pahhelgaasse' in Kashmiri. The plant is quite abundant and widespread throughout the world. Yarrow is terrestrial and is usually found in Alpine or subalpine zones, anthropogenic (man-made or disturbed habitats), cliffs, ridges, meadows and fields, mountain summits and plateaus, shores of rivers or lakes [2]. In India, it is found in Himalayas from Kashmir to Kumaun at the

altitude of 1050-3600 meters; also found in Mumbai and Belgaum areas. In Kashmir, Achillea millefolium is Commonly found throughout the Valley, Kishtwar (towards Symthan Pass), waste lands and in open mountainous slopes, etc [3].

Achillea millefolium L. is an erect, herbaceous perennial with a creeping rhizomatous (usually aromatic) form. The upright stems (0.2 – 1m tall) are fissured and downy covered with a clump of dark green feather like leaves which are finely pinnate (divided two to three times) with linear lobes [4]. The linear, lanceolate leaves are alternately arranged with each node bearing only one leaf. The plant, at its top, bears flat topped corymbs with densely clustered daisy-like flower heads. The tubular disc florets are whitish in colour, however, the strap-shaped ray florets may vary from white to pink to slightly reddish in colour. The fruit is an achene , compressed and slightly winged . The plant blooms from June to September and is visited by a huge range of insects [5]. The species is quite diverse and widely distributed throughout the world. There is a lot of variation in its ploidy level with diploid, tetraploid, hexaploid [6] and octaploid [7] cytotypes identified. The plant is a drought tolerant species and responds best to well drained a and poorly developed soils [8]. *Achillea millefolium L.* is mycotrophic and forms association with Arbuscular mycorrhizal fungi [9].

The plant has been exploited for its medicinal properties from times immemorial. The yarrow was used as a wound-herb back in the middle ages. However, the antiquity of the plant being used to heal wounds is credited to the Greek legend 'Achilles' after which the genus is named who employed it to heal the wound he himself inflicted on Telephus, king of Mysia. In the Anglo-saxon version of the herbarium of Apuleius Platonicus, this ascription had already been generalized, and common yarrow is specified as a herb that Achilles used to heal the wounds of his warriors, especially those who were wounded with iron [10]. Yarrow is one of the most antique remedial herb to be used by the ancients as its pollen was one among the six types found in the Neanderthal graves in Iraq dating back to 65,000 B.C.[11]. Yarrow is believed to have been used ritually and medicinally [12]. Dioscorides, in his 'De Material Medica' mentioned yarrow as an excellent remedy for ulcers, excessive blood discharge and for fistulas [13].

Due to its remarkable remedial properties as evidenced in traditional medicinal systems and from studies carried out on its pharmacology in the recent past, it is imperative to focus upon keeping an up-to-date knowledge of this medicinal herb. The presence of several bioactive compounds which have been so far discovered from this magical herb have confirmed its folklore utilization making it a promising candidate for future drug development. Multifold in-vivo and in-vitro pharmacological experiments with *Achillea millefolium L.* have proved its anti-spasmodic, anti-hepatic, anti-inflammatory, anticancer and anxiolytic-like activities etc. which hold excellent promises for its incorporation in modern drugs, besides substantiating the rationale behind its traditional use in curing complex diseases. The tremendous benefits derived from indigenous knowledge of this medicinal herb go largely uncredited. A thorough literature review based on different aspects such as biology, pharmacology and therapeutic activities of this valuable herb was done and the same has been reviewed in this article. These reports provide an insight into the huge medicinal potential of this plant suggesting that *Achillea millefolium L.* is a medicinal plant worthy of future investigation.

International Journal of Advance Research in Science and Engineering
Volume No.07, Special Issue No.04, March 2018
www.ijarse.com
IJARSE
ISSN: 2319-8354

1.1 Figures

Fig. (a) *Achillea millefolium L*. young plant **(b)** *Achillea millefolium L*. mature plant with flat-topped inflorescence **(c)** *Achillea millefolium L*. flowers **(d)** *Achillea millefolium L*. at mature stage **(e)** *Achillea millefolium L*. seeds.

2. Traditional uses

Parts used: Aerial parts, young leaves, dried flowers are used medicinally [14].

Harvesting: The young leaves can be harvested in the early days of spring when they are still soft, for use in soups and salads. Later they get too tough to be used fresh and should be dried. Leaves and flowers can be harvested until July/August when the plant is in full bloom [15].

Being a medicinal herb of high therapeutic repute, *Achillea millefolium L.* finds an extensive use in folk healing and traditional systems of medicine and official medicine as well [16*]. A. millefolium L*. is used to treat gastrointestinal disorders [17], skin inflammation, bleeding and wound healing [18]. A hot tea made from boiling the leaves is taken orally as a cure for headache, fever and urinary disorders. Chewing of fresh leaves relieves toothache [19]. Leaves and floral-heads are crushed to a paste and used as a remedy to cure inflammation in the gums [20]. An ointment made from yarrow can be used on ulcers [21]. A decoction of leaves prepared by steeping them is used to cure stomach disorders. A paste of leaf and flower extract, mixed with flour is used as antihemorrhagic and antipyretic. The extract is also administered externally as a poultice for treating rashes, cuts, bruises and snakebites [22] and dog bites [11]and heal them faster. Besides, a topical treatment prepared by making a paste of extract with corn flour is also applied to heal the wound and snakebites [23]. The flower taken as a decoction is laxative, diuretic, stimulant, tonic to the brain. The herb is useful in cold and fever, increases perspiration (Yarrow tea raises the temperature naturally and promotes perspiration)

[21] and purifies blood. A tea prepared from fresh leaves is used in colds and other ailments in children [24]. Leaves are crushed to cure dysentery, and a tincture is useful in treating urinary tract infections. Flowers are aromatic, carminative and are used to cure mumps, measles, and diabetes [25]. A tincture is also used to treat anxiety. The flowers of yarrow are also used as anthelmintic, anatriptic. Plant extract often used as nasal drops to treat nasal congestion [3].The stalk is used an an analgesic in the treatment for pain relief and the leaves in a steam inhalant for headaches. The roots are chewed and the saliva applied to appendages as a stimulant. An infusion of yarrow aids in restful sleep [8]. Yarrow finds its use as an adjuvant in the therapeutic preparations for many indications such as gynaecological agents, cardiac agents, preparation for varicose veins and convulsions [14]. The flower infusion of yarrow is traditionally used to cure digestive disorders and menstruation pain in Spain [26]. Other folklore uses of *Achillea millefolium L.* 'flower tops' include treatment of hematuria, leucorrhoea, menorrhagia, atonic amenorrhoea [27].

3. Pharmacology of *Achillea millefolium L.*

The essential oil extracted from *Achillea millefolium L.* has numerous phytochemical constituents including borneol, bornyl acetate (trace), camphor, 1.8-cineole, eucalyptol, limonene, sabine, terpin4-ol, terpineol and α-thujone (monoterpenes), caryophyllene (a sesquiterpene) achillicin, achillin, millefin and millefolide (sesquiterpene lactones), azulene and chamazulene (sesquiterpene lactone derived), and isoartemisia ketone [28] that have been explored after continued phytochemical investigations of traditional and folklore remedies. The European Pharmacopoeia shows the use of aqueous and alcoholic extract in the traditional European remedial drugs against inflammatory and spasmodic gastrointestinal disturbances, hepatic disorders, and as an appetiser [18]. Besides, yarrow has been a herb with common utilization in traditional medicine of several cultures from Europe to Asia for the treatment of a multitude of disorders. The essential oils of *Achillea millefolium L.* are chiefly composed of monoterpenes (constituting 90% of essential oils)[28]. Although, a wide diversity of chemical constituents have been reported so far. Some of the main phytochemical constituents that have been isolated from the plant are enlisted in Table 1.

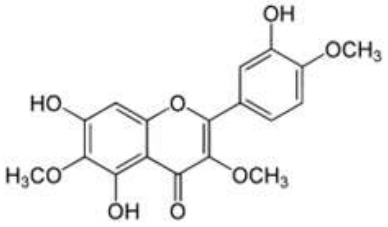
Table 1 Phytoconstituents reported from *Achillea millefolium L.*

Phytochemical class	Corresponding phytoconstituents	Detection methods	References
Asarones	Alpha-asarone	GC FID, GC-MS,	Falconieri(2011) [50]
Alkatrienes	Santolinatriene	GC-MS	Al- Abrass(2015) [51]
Esters	Bornyl acetate, Crhysanthenyl acetate	GC-MS, TLC.	Al- Abrass(2015) [51] Falconieri(2011)[50]
Ether	Eucalyptol (1,8-cineole)	GC-MS,	Al- Abrass(2015) [51] Candan F et al

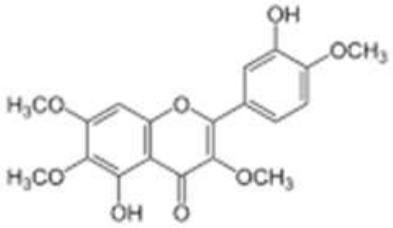
			(2003).[41]
Lactones	Coumarin, achillicin, achillin	GC/GC-MS. HPLC	Nascimento.(2000)[52]
Phenols	Eugenol , flavanol, Apigenin, luteolin, centaureidin, casticin artemetin, 1, 3-Dicaffeoylquinic acid, cynarin, quercetin, Rutin, 5-hydroxy-3,6,7,4′-tetramethoxyflavone	Steam distillation, GC/GC-MS, HR-MS spectra and 1D- and 2D-NMR techniques, HPLC, Column chromatography	Santroo. G.F (2007)[43] Nascimento.(2000)[52] Csupor-Löffler, (2009)[45], Lemmens-Gruber (2006)[53] Falk (1975)[54]
Terpenes	Monoterpenes: 1,8-cineole, camphor, borneol, α- and β-pinenes. Sesquiterpenes: chamazulene, β-caryophyllene	GC FID, GC-MS, Steam distillation. HR-MS spectra and 1D- and 2D-NMR techniques, SPME,	Falconieri(2011) [50], Nawras Al-Abrass. (2015)[51],Candan (2013)[41], Santroo. G.F (2007)[43], Nemeth, E. (2005)[55] Csupor-Löffler, (2009) [45], Jens (2000)[56] Figueiredo (1992)[57] Orav (2006)[58]

TLC thin-layer chromatography, *IR* infrared spectroscopy , *SPME* Solid-phase microextraction, *2D NMR* two-dimensional nuclear magnetic resonance, *HPLC* high-performance liquid chromatography, *MS* mass spectrometry, *GC-MS* gas chromatography mass spectrometry, *HR MS* high resolution mass spectrometry, *GC FID* gas chromatography with flame ionization detector

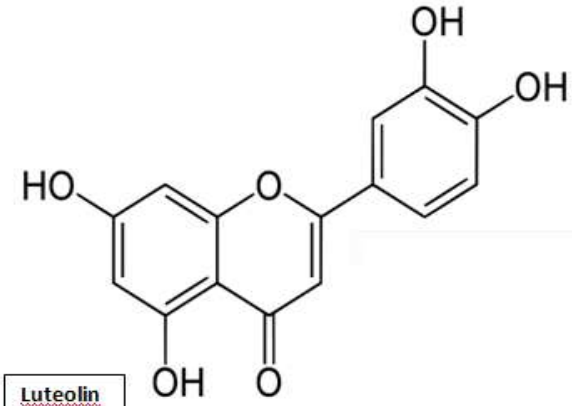
Luteolin



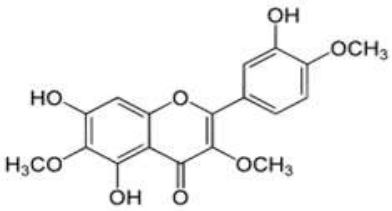
Centaureidin



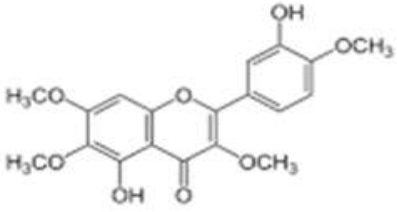
Casticin



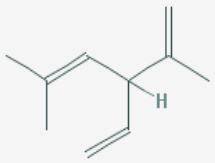
Luteolin



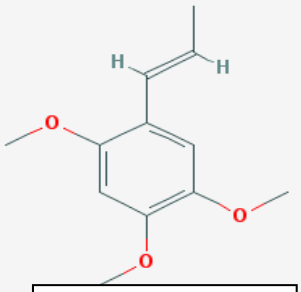
Centaureidin



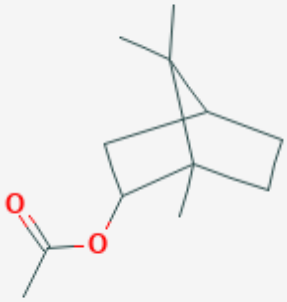
Casticin



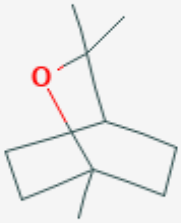
Santolina triene; 2,5-Dimethyl-3-vinyl-1,4-hexadiene.



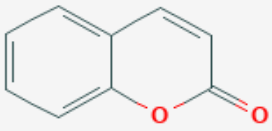
Asarone



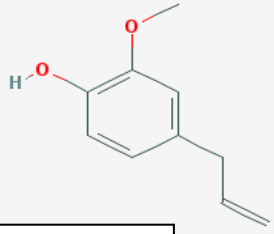
Bornyl acetate



Eucalyptol (1, 8-cineole)



Coumarin



Eugenol

Fig. 2 Representative bioactive compounds isolated from *Achillea millefolium L.*

Different pharmacological experiments carried out using in-vitro and in-vivo models have proven wide range use of *Achillea millefoilium L.* in traditional and folklore remedies [29]. A few of its pharmacognostic effects are summarised below.

3.1 Gastroprotective Activity

Experimentally induced stomach ulcers in rodents representing different characteristics of human ulcers indicated the involvement of protective mechanism of gastric mucosa when treated with aqueous extract of leaves of *Achillea millefolium L.*. The extract was found to protect gastric mucosa against the injury caused by the necrotic action of ethanol which leads to the damage of the mucous and bicarbonate gelatinous layer protecting the stomach. Also, the treatment with the aqueous extract showed considerable reduction in the volume and acidity caused by the secreted gastric juices suggesting a blockage of the principle receptors of the parietal cells (M_3, H_2 – Histamine receptor and CCKb –gastrine receptor) and well as their secondary messengers. As such the extract of *Achillea millefolium L.*is attributed with effective protection of gastric mucosa and inhibition of gastric secretions thereby confirming its use as a folklore remedy against gastrointestinal disorders [30].

3.2 Anxiolytic-like Activity

Hydroalcoholic extract of the aerial parts of *Achillea millefolium L.* was tested in various animal models for its anxiolytic-like effects. The Swiss albino mice were subjected to 'elevated plus maze' and 'marble burying test' after administering *Achillea millefolium L.* extract at doses that didn't alter locomotor activity. The mice were checked for the behavioural profile after repeating the treatment for 25 days. The extract was shown to deliver anxiolytic-like drug behaviour similar to diazepam due the absence of tolerance in mice after short term repeated treatment with Hydroalcoholic extract of *Achillea millefolium L.* flower [31]. The mode of action of *Achillea millefolium L.* extract is suggested to be via non-BDZ/γ-aminobutyric acid mechanism which is an essential feature differentiating it from the most widely recommended anxiety relieving drugs, the benzodiazepines and from other plants showing similar effects [32]. Thus, *Achillea millefolium L.* may prove to be promising in the development of a new class of anxiolytic drugs.

3.3 Hepatoprotective Activity

Liver is the most important organ of the human body as it performs a wide array of essential functions in regulating the homeostatis and overall metabolism of the body. A study was carried out on mice treated with CCL_4 and given a pre-treatment of aqueous and alcoholic extract of *Achillea millefolium L.*. The pre-treatment given to mice showed significant reduction in the levels of ALT (alanine aminotransferase), AST (aspartate aminotransferase) and ALP (alkaline phosphatase) in plasma mainly induced by D- galactosamine [33]. The results hint at a calcium channel blocking activity which may be attributed to hepatoprotective effects of the extract of *Achillea millefolium L* [34]. CCL_4 induced liver damage in the animal models resulted in severe

hepatotoxicity due to tissue degeneration and necrosis of liver due to which it produced abnormally high levels of liver enzymes. This resulted in oxidative stress due to increased levels of ROS and decreased levels of anti-oxidants. *Achillea millefolium L.* constitutes a wide range of bio-active compounds including flavanoids – a strong anti-oxidant. The degree of protection of structural integrity of liver of the CCL_4 infected mice, as verified by histopathology, was determined when the mice were treated with methanolic extract of *Achillea millefolium L.* proving the herb's hepatoprotective activity [33]. These experiments have proven useful in rationalising the folk uses of the herb in treating the hepatic disorders and hints at its use in modern drug industry against liver abnormalities.

3.4 Wound-healing Activity

Due to the presence of active principles like alkaloids, terpenes, flavanoids etc. *Achillea millefolium L.* possesses therapeutic potential to heal wounds. In a study carried out on Wistar albino rats, the aqueous and alcoholic extracts of the powdered leaves of *Achillea millefolium L.* significantly accelerated the wound healing activity besides acting as a blood coagulant. Rats with wounds inflicted subcutaneously were administered an oral 200mg/kg dose of *Achillea millefolium L.* extract for 10 days continuously. The histological examination and the statistical analysis of the granuloma tissue showed increased collegen content compared to control confirming the positive effect of the extract on wound healing [35]. In another study, rats were treated with 10% dose of *A. millefolium L.* extract after making surgical wounds in them. The rats were analysed for 28 days and biopsies were conducted and the data analysed showed that collagen fibres were abundant more organised. Hence *A. millefoilium L.* extracts were shown to have better activity on healing inflamed cuts or wounds compared to other extracts like zinc oxide [36].

3.5 Anti-inflammatory Activity

The antiphlogistic activity can be attributed to the flavanoids present in *Achillea millefoilium L.* . Flavonoids contribute to the anti-inflammatory activity by inhibiting the human neutrophil elastase (HNE)and matrix metalloproteinases (MMP -2 and -9) as was found in a study carried out to test the crude plant extract for understanding antiphlogistic mechanisms in *Achillea millefoilium L.* [37]. Similar results were found when mice were subjected to mouse paw edema test and treated with an aqueous extract of *A. millefoilium L.* The results showed a 35% reduction in the inflammation [38]. Azulenes, the major component of *A. millefoilium L.* are powerful anti-inflammation agents contributes to the plant's antiphlogistic activity alonwith lactones and sesquiterpenes [39]. Thus, the above result could give an insight into the pharmacological activity of Achillea millefolium L. which could eventually lead to the isolation and development of novel medicines to treat acute and chronic inflammatory ailments.

3.6 Anti-oxidant Activity

Achillea millefolium L. aqueous extract has the principle compounds which act as free radical scavengers. The phenolic content in the flower extract of *A. millefolium L.* showed considerable reduction in intracellular

Reactive Oxygen species [40]. The plant extracts have been found to reduce diphenylpicrylhydrazyl radicals and act as hydroxyl radical scavenger in Fe^{3+}-EDTA-H_2O environment. The extract also halted non-enzymatic lipid peroxidation in rat liver [41]. The oral administration of *A. millefolium L.* to rats exposed to ulcer agents (acetic acid and ethanol) prevented chronic gastric ulcers and triggered gastric mucosa regeneration after ulcer induction. This protective effect was attributed to the anti-oxidant properties of the plant [42].

3.7 Anti-microbial and Anti-parasitic Activity

The oil of the plant has been effective against various microbes such as *Streptococcus pneumoniae, Clostridium perfringens, Candida albicans, Mycobacterium smegmatis, Acinetobacter lwoffii and Candida krusei* [41] and hence its use in antibiotics could revolutionize the drug industry. The growth of an euglenoid, *Trypanosoma cruzi* (feeds on blood and lymph of humans , horses and cattle) has been found to be inhibited by the oil of the plant [43]. The plant has been exploited traditionally to cure many microbial and parasitic diseases. This has however also been proven scientifically and many reports are present to validate this. The plant extracts have proven to significantly reduce egg count of nematodes in sheep. Thereby, the plant can be used as a potential cure to treat helminth infection in ruminants and can serve as an effective vermifuge [44].

3.8 Anti-tumour Activity

MMt assays were carried out on three tumour cell lines (HeLa, MCF-7 and A431) to examine anti tumour activity of *A. millefolium L.*. Centauredin , a flavonoid was found to have significant effect on the inhibition of cell growth in HeLa and MCF cells. Other phytochemical constituents Apigenin, Luteolin, and isopaulitin were also found to possess anti-cancerous activity though not as high as Centauredin. However, Artementin, Psilostachin C, disacetylmaticarin and sinetin failed to show any such activity [45]. A study carried out on Mouse with Leukemia revealed that three sesquiterpenoids viz Achimillic acid A, B, C proved to be effective against mouse p-388 leukemia cells in vivo thereby acting as anti-tumour agents [46]. Casticin, an another flavonoid found in the extracts of this plant has been found to show anti-proliferative activity by arresting cell growth in G2/M phase and leading to cell death by inducing apoptopsis. It acts by binding to tubulin, inhibits activity of cdK1 and downregulates cyclin A [47]. All these results indicate the use of *A. millefolium L.* in cancer therapy with promising results.

3.9 Estrogenic Activity

The plant has been traditionally used to cure menstrual disorders [48]. The natives of Europe and Northern America used it as a contraceptive, emmenagogue and as an abortive medicine [49]. This traditional use has been justified by a study revealing that the phytochemicals, apigenin and luteolin present in the plant lead to the activation of α and β estrogen (ERα and ERβ) receptors leading to high estrogenic activity and high menstrual flow. This property of *A. millefolium L.* could be put to use as a novel way of treating menstrual disorders.

4. Conclusion

With an ever increasing rate of lifestyle related diseases and chronic health challenges being on the rise, the healthcare services are struggling to keep pace with the rational accelerating curative health management demands and to deliver an optimal therapeutic environment supporting better treatments and wellbeing to meet the ever changing needs of a growing population and its healthcare. In this context, identification of novel active phytochemical compounds is essential to combat ever increasing disease rates especially deadly diseases like cancers and their ilk. Reconsidering botanicals for their active medicinal ingredients may address some of these emerging health issues. In order to improve the quality of healthcare, the medicinal plants which have long been used in traditional medicine need to be investigated scientifically. Pertinently, the medicinal plant extract and essential oil of *Achillea millefolium L.*isan important and potent source of novel bioactive compounds which can be used in pharmaceuticals or as alternative medicine to synthetic drugs and in natural therapies for a spectrum of health ailments.

The present review, highlights the main pharmacognostic properties of Achillea millefolium L., a magical herb rightly regarded as a Cure-all for its potential to treat several health issues ranging from flu and fever to its use as a potential anti-cancer drug. Only those pharmacognostic properties of A. millefolium are noted in this review which have been reported after proper examination and investigation on the basis of scientific in-vitro, in-vivo and clinical evaluations. However, there are still unknown aspects of this plant that are worthy of attention and examination. Due to noteworthy pharmacological and pharmacognostic activities of *A. millefolium L.*, its use in the drug industry as a better option in the novel drug development with a different mode of action can be taken into consideration. The plant as a medicinal remedy has a lot of potential which still needs to be explored and exploited so that it could be put to use for the betterment of human kind. In addition to this, an extensive and rigorous investigation needs to be done on bioavailability and toxicity levels and contraindications of the plant as well as to explore and understand the pharmacodynamic and pharmacokinetic mechanisms of the rich reservoir of phytoconstituents of *Achillea millefolium L.* which could prove pharmacologically much efficient to be used as principal scaffold in modern drug industry.

REFERENCES

[1]. Simonetti, G., & Schuler, S. (1990). *Simon & Schuster's Guide to Herbs and Spices.* : Simon & Schuster, Inc.

[2]. Gobotany. from New England Wild Flower Society https://gobotany.newenglandwild.org

[3]. Rasool, S., Khan, M. H., Hamid, S., Sultan, P., Qazi, P. H., & Butt, T. (2016). *An overview and economical importance of few selected endangered medicinal plants grown in Jammu and Kashmir region of India.* Annals of Phytomedicine, *5(2), 27-37.*

[4]. Singh, M. P., & Panda, H. (2006). *Medicinal Herbs With Their Formulations*.

[5]. Clapham, A. R., Tutin, T. G., & D.M., M. (Eds.). (1987). *Flora of the british Isles* (3rd ed.). Cambridge: Cambridge University Press.

[6]. Small, E., & Catling, P. M. (1999). *Canadian Medicinal Crops* National Research Council Canada. from NRC Research Press

[7]. López-Vinyallonga, S., Soriano, I., Susanna, A., Montserra, J. M., Roquet, C., & Garcia-Jacas, N. (2015). *The Polyploid Series of the Achillea millefolium Aggregate in the Iberian Peninsula Investigated Using Microsatellites.*

[8]. *USDA,NRCS-PlantFactSheet*. (2003). Retrieved from: https://plants.usda.gov/factsheet/pdf/fs_acmi2.pdf

[9]. Allison, V. J. (2002*).* Nutrients, arbuscular mycorrhizas and competition interact to influence seed production and germination success in Achillea millefolium. Functional Ecology, *16, 742–749. doi:10.1046/j.1365-2435.2002.00675.x*

[10]. Grigson, G. (1955). *The Englishman's Flora.* Phoenix House, London.

[11]. Applequist, W., Moerman, D. E., & (2011*).* "Yarrow (Achillea millefolium L.) A Neglected Panacea?A Review of Ethnobotany, Bioactivity and Biomedical Research, ". *Economic Botany 65(2).*

[12]. Medicinal Plants, from traditional knowledge to scientific research. (2017). Retrieved from www.catalyststudent.org

[13]. Dioscorides, P. *De Materia Medica* (T. A. Osbaldeston & R. P. Wood, Trans.): IBIDIS Press.

[14]. *PDR for Herbal Medicines*. (2000). Medical Economics Company, Inc. Montavale, NJ.

[15]. Sacred Earth – History and Uses of Yarrow (*Achillea millefolium*) www.sacredearth.com/ethnobotany/plantprofiles/yarrow.php

[16]. F. Chandler, R., N. Hooper, S., & J. Harvey, M. (1982). Ethnobotany and phytochemistry of yarrow, Achillea millefolium, Compositae *(Vol. 36).*

[17]. Düsman, E., Almeida, I. V. d., Coelho, A. C., Balbi, T. J., Tatiani, L., Tonin, D., & Vicentini, V. E. P. (2013). Antimutagenic Effect of Medicinal Plants Achillea millefolium and Bauhinia forficata In Vivo.

[18]. B, B., & B, K. (2007). Achillea millefolium L. s.l. revisited: recent findings confirm the traditional use. *Wien Med Wochenschr.*

[19]. Yousuf, J., Verma, R. K., & Dar, H. (2012). Traditional plant based therapy among rural communities of some villages of Baramulla district (Jammu and Kashmir*). Journal of Phytology 4(5), 46-49.*

[20]. Kumari, S., Batish, D. R., Singh, H. P., Negi, K., & Kohli1, R. K. (2013). An ethnobotanical survey of medicinal plants used by Gujjar Community of Trikuta Hills in Jammu and Kashmir, India. *Journal of Medicinal Plants Research.*

[21]. Francks, J., & M.H. (2017). Yarrow (Achillea millefolium). Herbal Legacy Articles

[22]. Sheikh, M. A., Chishti, S., & Chishti, N. T. N. (2016). Medicinally Important Plants From Ganderbal, Kashmir, India- An Ethnomedicinal Survey. . *European Journal Of Pharmaceutical And Medical Research, ejpmr, 3(4),* 176-183.

[23]. Malik, A. H., Khuroo, A. A., Dar, G., & Khan, Z. (2011). Ethnomedicinal uses of some plants in the Kashmir Himalaya Indian Journal of Traditional Knowledge *10(2),* 362-366.

[24]. Mahajan, V., Vaid, A., A.P.Singh, & Kumar, S. (2016). Ethnobotanical Inventory on Medicinal Plants of North Western Himalayas, Journal of Krishi Vigyan.

[25]. Kaur, M., Singhal, V. K., & Singh, J. (2017). Use of some ethnomedicinal herbs by the natives of Solang valley, Kullu district, Himachal Pradesh. *Int J Pharm Pharm Sci*, *9*(9), 222-227.

[26]. Víctor López, Silvia Akerreta, Esther Casanova, Jose García-Mina, RitaCavero & Maria Calvo (2008) Screening of Spanish Medicinal Plants for Antioxidant and AntifungalActivities, *Pharmaceutical Biology*, *46:9*, 602-609, DOI: 10.1080/13880200802179634

[27]. Masood, A., Akbar, S., Masood, A., & Ganai, B. (2010). *Medicinal and Aromatic Plants from Kashmir Himalayas*.

[28]. Assessment report on Achillea millefolium L., flos, (2011). European Medicines Agency

[29]. SI, A., B, G., & V., V. (2017). Pharmacognosy, Phytochemistry and Pharmacological Properties of Achillea millefolium L.: A Review. *Epub Phytother Res. 2017*. doi:10.1002/ptr.5840.

[30]. Baggio, C. H., Freitas, C. S., Nhaducue, P. F., Rieck, L., & Marques, M. C. A. (2002). Action of crude aqueous extract of leaves of Achillea millefolium L. (Compositae) on gastrointestinal tract. *Rev. bras. farmacogn*, *12*.

[31]. Baretta et.al., (2012). Anxiolytic-like effects of acute and chronic treatment with Achillea millefolium L. extract *Elsevier 'Journal of Ethnopharmacology, 140*(1), 46-54.

[32]. Houghton, P. J. (1999). The scientific basis for the reputed activity of Valerian. *Journal of Pharmacy and Pharmacology*, *51*, 505-512.

[33]. Al-Ezzy, R. M., Anee, R. S. A. A., & Kathum, O. A. (2017). Hepatoprotective Effects of Achillea millefolium methanolic extract on carbon tetrachloride induced hepatotoxicity on albino male mice. *Int-.Adv.Res Biol.Sci*, *4*(8), 98-109.

[34]. S, Y., Jamal Q, K. A., & AH., G. (2006). Studies on hepatoprotective, antispasmodic and calcium antagonist activities of the aqueous-methanol extract of Achillea millefolium. *Phytother Res 2006*, *20*(7), 546-551.

[35]. Nirmala, S., & Karthiyayini, T. (2011).Wound Heaing Activity On The Leaves Of *Achillea millefolium* L. by Excision, Incision and Dead Space Model On Adult Wistar Albino Rats. *International Research Journal Of Pharmacy*.

[36]. Rezaie, A., Mohajeri, D., Valilou, M., Mousavi, G., Nazeri, M., Mohammadi, B., & Zakhireh, S. (2012). Geometric and Histopathologic Assessment of Yarrow Extracts(Achillea millefolium) and on Healing of Experimental Skin Wounds and its Comparison with Zinc Oxide on Rats. *Current Research Journal of Biological Sciences*, *4*(1), 90-95.

[37]. B, B., B, K., & MF, M. (2007). Achillea millefolium L. s.l. -- is the anti-inflammatory activity mediated by protease inhibition? . *J Ethnopharmacol.*, *113*(2).

[38]. Goldberg, A. S., Muller, E. C., Eigen, E., & Desalva, S. J. (1969). Isolation of the anti-inflammatory principles from Achillea millefolium (compositae) *journal of pharmaceutical sciences*, *58*(8), 938–941.

[39]. Alonso, J. (2004). *Tratado de Fitofármacos y Nutracéuticos. Barcelona*.

[40]. Burk, D. R., A, Z., Cichacz, & Daskalova, S. M. (2010). Aqueous extract of Achillea millefolium L. (Asteraceae) inflorescences suppresses lipopolysaccharide-induced inflammatory responses in RAW 264.7murine macrophages *Journal of Medicinal Plants Research*, *4*(3), 225-234.

[41]. Candan F et al (2003). Antioxidant and antimicrobial activity of the essential oil and methanol extracts of *Achillea millefolium* subsp. millefolium Afan. (Asteraceae). *Journal of Ethnopharmacology. 87*,pp 215-220

[42]. Potrich F.B et al (2010) .Antiulcerogenic activity of hydroalcoholic extract of *Achillea millefolium L.*: Involvement of the antioxidant system *130*, pp 85-92

[43]. Santoro G.F *et al* (2007) Trypanosoma cruzi: Activity of essential oils from Achillea millefolium L., Syzygium aromaticum L. and Ocimum basilicum L. on epimastigotes and trypomastigotes. *Experimental Parasitology 116*, pp 283-290

[44]. Tariq, K., Chishti, M., Ahmad, F., & Shawl, A. (2008). Anthelmintic efficacy of Achillea millifolium against gastrointestinal nematodes of sheep: In vitro and in vivo studies. *Journal of Helminthology, 82(3)*, 227-233.

[45]. Csupor-Löffler, B., Hajdú, Z., Zupkó, I., Réthy, B., Falkay, G., Forgo, P. and Hohmann, J. (2009), Antiproliferative effect of flavonoids and sesquiterpenoids from Achillea millefolium s.l. on cultured human tumour cell lines. *Phytother. Res., 23*: 672–676.

[46]. Tozyo et al, (1994) Novel Antitumor Sesquiterpenoids in Achillea millefolium.*Chemical and Pharmaceutical Bulletin Volume 42 (1994) Issue 5*

[47]. Haïdara, Khadidja et al (2006). The flavonoid Casticin has multiple mechanisms of tumor cytotoxicity action. *Cancer Letters , Volume 242 , Issue 2* , 180 – 190

[48]. Akram, M. J Membrane Biol (2013) 246: 661. https://doi.org/10.1007/s00232-013-9588-x

[49]. Saeidnia, S., Gohari, A., Mokhber-Dezfuli, N., & Kiuchi, F. (2011). A review on phytochemistry and medicinal properties of the genus Achillea. DARU : *Journal of Faculty of Pharmacy, Tehran University of Medical Sciences, 19(3)*, 173–186.

References listed in Table

[50]. Falconieri D, Piras A , Porcedda S , Marongiu B , Gonçalves MJ , Cabral C , Cavaleiro C , Salgueiro L (2011), Chemical composition and biological activity of the volatile extracts of Achillea millefolium.. *Natural Product Communications [01 Oct 2011, 6(10):1527-1530]*

[51]. Al- Abrass N.(2015) Chemical Composition and Antimicrobial Activity of the Essential Oils of Achillia falcata L. (Asteraceae). *International Journal of PharmTech Research, 7*, pp 41- 46.

[52]. Nascimento, G.G.F (2000). Antibacterial activity of plant extracts and phytochemicals on antibiotic-resistant bacteria. Braz. J. *Microbiol. vol.31* .

[53]. Lemmens-Gruber R et al, 2006; Investigation of the Spasmolytic Activity of the Flavonoid Fraction of Achillea millefolium s.l. on Isolated Guinea-pig Ilea56(8): 582-588

[54]. Falk, A. J., Smolenski, S. J., Bauer, L. and Bell, C. L. (1975), Isolation and identification of three new flavones from Achillea millefolium L.. J. Pharm. Sci., 64: 1838–1842.

[55]. Nemeth, E. (2005). Essential Oil Composition of Species in the Genus Achillea. *Journal of Essential Oil Research, 17*(5), 501-512. doi:10.1080/10412905.2005.9698978

[56]. Jens Rohloff, Else Berit Skagen, Albert Haakon Steen, and Tor-Henning Iversen (2000). Production of Yarrow (*Achillea millefolium L.)* in Norway: *Essential Oil Content and QualityAgric. Food Chem., 48 (12), pp 6205–6209*

[57]. Figueiredo, A. C., Barroso, J. G., Pais, M. S. S. and Scheffer, J. J. C. (1992), Composition of the Essential Oils from Leaves and Flowers of Achillea millefolium L. ssp. millefolium. *Flavour Fragr. J., 7: 219–222.*

[58]. Anne Orav, Elmar Arak & Ain Raal (2007) Phytochemical analysis of the essential oil of Achillea millefolium L. from various European Countries, *Natural Product Research, 20:12, 1082-1088,*