Medicinal plants as a source of future anti-pruritic drugs: A comprehensive review

[Fahimeh Mohajerani, Mannan Hajimahmoodi, Laila Shirbeigi & Roja Rahimi]

Abstract: Pruritus is a distressing sensation of the skin that provokes the desire to scratch. Medicinal plants have been proposed as a worthful source for identifying new bioactive molecules. The aim of this study was to evaluate some medicinal plants and their phytochemicals used in the management of pruritus. Medicinal plants including Avena sativa, Borago officinalis, Capsicum frutescens, Curcuma longa, Fumaria spp., Mentha x piperita and Oenothera biennis showed the promising anti-pruritic activity in human studies. In experimental studies, Angelica sinensis, Betula platyphylla, Matricaria chamomilla, Rumex Japonicus, Saururus chinensis and Vaccinium myrtillus are among the best medicinal plants for management of pruritus. Essential oils, alkaloids, saponins, sterols, terpenes, phenolic compounds, and fatty acids were the bioactive constituents of herbs which exhibited their anti-pruritic activity through different mechanisms. The most predominant mechanisms involved in activity of plant-derived molecules in pruritis include reducing serum IgE and proinflammatory cytokines, stabilizing mast cells, suppressing the Th2 cellular response, suppressing the expression of substance P and NF-κB, inhibiting prostaglandin E2 production, and activating receptors involved in itch sensation. Overall, several medicinal plants and its bioactive compounds have shown marked activity in the management of pruritus and therefore can be considered as an alternative source of treatment.

Keywords: Itch; Pruritus; Plant; Scratch; Herbal medicine; Phytochemical

Resumen: El prurito es una sensación molesta en la piel que provoca el deseo de rascarse. Las plantas medicinales han sido propuestas como una fuente valiosa para identificar nuevas moléculas bioactivas. El objetivo de este estudio fue evaluar algunas plantas medicinales y sus fitoquímicos en el manejo del prurito. Plantas medicinales que incluyen Avena sativa, Borago officinalis, Capsicum frutescens, Curcuma longa, Fumaria spp., Mentha x piperita y Oenothera biennis mostraron una prometedora actividad antiprurítica en estudios humanos. En estudios experimentales, Angelica sinensis, Betula platyphylla, Matricaria chamomilla, Rumex Japonicus, Saururus chinensis y Vaccinium myrtillus se encuentran entre las mejores plantas medicinales para el manejo del prurito. Los aceites esenciales, alcaloides, saponinas, esteroides, terpenos, compuestos fenólicos y ácidos grasos fueron los constituyentes bioactivos de las hierbas que mostraron actividad antiprurítica a través de diferentes mecanismos. Los mecanismos más predominantes implicados en la actividad de las moléculas derivadas de plantas en el prurito incluyen la reducción de la IgE sérica y las citoquinas proinflamatorias, la estabilización de los mastocitos, la supresión de la respuesta celular Th2, la supresión de la expresión de la sustancia P y NF-κB, la inhibición de la producción de prostaglandina E2 y la activación de receptores implicados en la sensación de picazón. En general, varias plantas medicinales y sus compuestos bioactivos han mostrado una actividad efectiva en el manejo del prurito y, por lo tanto, pueden ser consideradas como una fuente alternativa para su tratamiento.

Palabras clave: Picazón; Prurito; Planta; Rascar; Medicina herbaria; Fitoquímico
LIST OF ABBREVIATIONS
AD: Atopic dermatitis; CU: Chronic urticaria; CU-QoL: Chronic urticaria quality of life questionnaire; DNCB: 2, 4-dinitrochlorobenzene; hs-CRP: highsensitivity C-reactive protein; IFN-γ: Interferon gamma; IgE: Immunoglobulin E; IL: Interleukin; NF-κB: Nuclear factor-kappa light-chain enhancer of activated B cells; PG102: A general term for various preparations from Actinidia arguta; PG102E: Ethylacetate-soluble fraction from PG102T; PG102T: Total water-soluble extract from Actinidia arguta; QoL: quality of life; SP: Substance P; T½: T-helper cell type 2; TNF-α: Tumor necrosis factor alpha; TRPM8: Transient receptor potential cation channel, subfamily M, member 8; TRPV1: Transient receptor potential vanilloid 1; UAS: Urticaria activity score.

INTRODUCTION
Skin disorders are one of the most common health problems among people, causing emotional and psychological stress. These disorders account for approximately 34% of all occupational diseases encountered worldwide (Goyal et al., 2014; Maurya & Seth, 2014). Pruritus or itch is an irritating and unpleasant sensation which produces a desire of scratching. Chronic itching can be severe enough to cause negative interference with many aspects of life. In addition, induced scratching behavior often leads to secondary lesions which can be followed by cutaneous infections (Ikoma et al., 2006).

Data on the prevalence of pruritus demonstrated 8-9% people experienced acute pruritus during their life (Rea et al., 1976; Dalgard et al., 2004). Recent studies showed higher prevalence of pruritus even around 13.5% in the general adult population (Dalgard et al., 2007; Matterne et al., 2011). Despite the high prevalence of pruritus, it has not received much attention until recently (Goyal et al., 2014; Maurya & Seth, 2014).

Pruritus has various etiologies and pathophysiologicals. It can be as a characteristic feature of numerous skin diseases or as an unusual sign of certain systemic and neurological diseases. It can also arise from dry skin, especially in cold winter months. Pruritus may be localized or generalized and can occur both acutely and chronically. Localized pruritus appears in the skin disorders especially in different types of dermatitis. Generalized pruritus may be consequence of environmental factors including low humidity, skin diseases such as urticaria, or internal diseases including biliary obstruction, renal failure, hematologic malignancy or acquired immunodeficiency syndrome (Sänder et al., 2007). Extreme pruritus often results in secondary lesions such as erythema, erosions and crusts, followed by cutaneous infections (Waisshaar et al., 2003).

Pathophysiology of Pruritus
Various pathological processes are involved in pruritus: inflammation, hypersensitivity, degenerative changes, malignant tumors, and even psychic abnormalities (Goyal et al., 2014). Neurophysiological experiments in humans and animals have exhibited that itch is carried by specific C nerve fibers (Yosipovitch & Fleischer, 2003). The sensation of itch is transmitted through specific peripheral unmyelinated C-fiber nerves in which are located in the epidermis and dermis. These neurons are located more superficially and are more sensitive to pruritogenic substances (Goyal et al., 2014). These C-fiber nerves also called prurceptors are a subclass of C-nociceptors for pain, but functionally different from pain fibers (Twycross et al., 2003). The symptom of itch occurs when free nerve endings of the specialized C-fibers are stimulated by pruritogenic substances.

A number of endogenous and exogenous pruritogens (itch triggers) have been identified. The pruritogenic mediators are mentioned in Table No. 1. Furthermore, other endogenous pruritogens and different exogenous pruritogens and also their mechanisms of action are mentioned in Table No. 2 and Table No. 3, respectively.

Management/Treatment of Pruritus
Anti-pruritic strategy could be assigned according to the underlying causes of different categories of itch (Yosipovitch & Fleischer, 2003). Treatment options include non-pharmacological and pharmacological measures (Goyal et al., 2014). Non-pharmacological treatments include life style modifications and diet. Pharmacological strategies consist of topical and systemic treatments.

Topical Therapy
Topical therapies contain emollients, topical corticosteroids, and Topical calcineurin inhibitors.
Table No. 1
Different pruritogenic mechanisms of mediators

<table>
<thead>
<tr>
<th>Mediators</th>
<th>Site of release</th>
<th>Pruritogenic mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>Histamine H1 receptor</td>
<td>Activating the cutaneous C-fibres</td>
</tr>
<tr>
<td>Acetylcholine (neurotransmitter)</td>
<td>Muscarinic and nicotinergic receptors</td>
<td>Causes itch only in atopic persons (but not in non-atopic persons)</td>
</tr>
<tr>
<td>Serotonin (a mediator in psychogenic itch)</td>
<td>5-HT3 receptors</td>
<td>A potent activator of unmyelinated C-fibres</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>-</td>
<td>Induces mast-cell degranulation for the release of histamine and enhances histamine responses</td>
</tr>
<tr>
<td>Prostaglandins</td>
<td>-</td>
<td>Potentiate histamine-induced itch by lowering the receptor threshold to histamine and papain</td>
</tr>
<tr>
<td>Cytokines: Interleukins (IL-2, IL-4, IL-6 and IL-31)</td>
<td>T cells and macrophages</td>
<td>Activating the cutaneous C-fibres</td>
</tr>
</tbody>
</table>

Table No. 2
Endogenous pruritogens and their mechanisms of action

<table>
<thead>
<tr>
<th>Endogenous pruritogen</th>
<th>Pruritogenic mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve growth factor</td>
<td>Sensitization of peripheral nerve fibers</td>
</tr>
<tr>
<td>Substance P (SP), Calcitonin gene-related peptide (CGRP)</td>
<td>Acute pro-inflammatory reactions including vasodilatation and protein extravasation, trophic function and immunomodulation</td>
</tr>
<tr>
<td>Endogenous opioids: enkephalin, β- endorphin (through stimulation of mu receptors)</td>
<td>Modulation the sensation of pruritus both centrally and peripherally</td>
</tr>
<tr>
<td>Stress</td>
<td>Modification of expressing the inflammatory cytokines by mast cells</td>
</tr>
</tbody>
</table>

**Systemic Therapy**
Systemic therapies include antihistamines, systemic corticosteroids, immunomodulators, interferon gamma, monoclonal antibodies, and immunosuppressants.

However inadequate efficacy, high rate of recurrence and the suppression of immune system, and hepatic and renal toxicity have limited their use in the treatment of this syndrome. Hence, the management of pruritic conditions remains a therapeutic challenge due to its multifactorial etiology and complex pathophysiology (Goyal *et al.*, 2014; Maurya & Seth, 2014).

**Prospect**
The use of medicinal plants as complementary or alternative strategy for management of diseases especially chronic conditions is arising (Farzaei *et al.*, 2014).
2013; Mobli et al., 2015). Plant-derived compounds or phytochemicals are assumed as an invaluable source for discovering new pharmaceutical agents (Farzaei et al., 2016a; Farzaei et al., 2016b; Shahpiri et al., 2016).

Purpose of the Present Study
The aim of present study is to comprehensively review medicinal plants with well-established activities in pruritus and discuss their possible underlying mechanisms.

### Table No. 3
Different Exogenous Pruritogens

<table>
<thead>
<tr>
<th>Chemical stimuli</th>
<th>Physical stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botanicals: poison ivy, stinging nettles, and cowhage spicules</td>
<td>Light touch, pressure, and suction</td>
</tr>
<tr>
<td>Latex (a plant derivative)</td>
<td>Heat</td>
</tr>
<tr>
<td>Cosmetics and soaps</td>
<td>Electrical stimulation</td>
</tr>
<tr>
<td>Insect bites</td>
<td>Wool fibers</td>
</tr>
<tr>
<td>Parasite infestations (ie, scabies)</td>
<td>Fiberglass</td>
</tr>
<tr>
<td>Drugs: opiates, aspirin, and β-blockers</td>
<td>Water (“aquagenic pruritus”)</td>
</tr>
<tr>
<td>Chemical stimuli</td>
<td>Physical stimuli</td>
</tr>
</tbody>
</table>

Research method
In this article it has been focused on the use of medicinal plants in various dermatological conditions characterized by pruritus. For this purpose, online searches were conducted in electronic databases including English-language papers published up to 2018 in PubMed, MEDLINE, Scopus, Google Scholar, Science Direct and reference lists of retrieved articles from 1960s to 2018 (up to May) for any in vitro, animal or clinical studies investigating the efficacy of a medicinal plant or its bioactive component in managing of pruritus. The searched keywords were “plant”, “herb”, “extract”, “itch”, “pruritus”, “scratch” and “anti-pruritic”. The title and abstract of each article were examined to eliminate duplicates.

Anti-pruritic medicinal plants and their bioactive components for managing pruritus
The medicinal plants studied in this review are arranged alphabetically according to their scientific name, followed by family name, parts used, growing area, related clinical trials, main bioactive components, and probable mechanism of anti-pruritic effect.

**Aloe vera**
*Aloe vera* (L.) Burm.f. commonly known as *Aloe vera* (Family: Xanthorrhoeaceae) is a shrub originated in the Sudan and the Arabian Peninsula and is now found in various regions of the world (Fleming, 2000). A study investigating the effects of oral *Aloe vera* gel (AV) on atopic dermatitis mice with the symptoms like itching demonstrated relief in AD due to reduction of interleukin (IL)-5 and IL-10 levels (Kim et al., 2010). In a double-blind placebo-controlled study, 60 patients with mild to moderate plaque psoriasis were topically treated with either 0.5% hydrophilic Aloe cream or placebo. The Aloe-treated group showed marked improvement (83.3%) compared to the placebo group (6.6%). No adverse events were reported in the treatment group (Syed et al., 1996). Inhibition of Cox-2 and thromboxanes by aloeisin was revealed in vitro (Yagi et al., 2002). A topical mixture of *A. ferox* and *A. vera* extracts decreased the serum level of IgE in an atopic dermatitis mouse model (Finberg et al., 2015). Fresh *Aloe vera* Gel significantly reduced acute inflammation in rats (carrageenan-induced paw edema). The anti-inflammatory effect of the Aloe gel has been related to its enzymes, carbohydrates and sterols contents. Bradykinase inhibited thromboxane B2 and prostaglandin F2 activity *in vitro*, and mannose-6-phosphate, acemannan and sterols (mainly lupeol) reduced inflammation *in vivo* (Choi & Chung, 2003).

**Actinidia arguta**
*Actinidia arguta* (Siebold & Zucc.) Planch. Ex Miq. with the common name of Hardy Kiwi (Family: Actinidiaceae) is a perennial plant native to eastern Asia and Russian Siberia (Park et al., 2007).
Administration of oral formulas from *Actinidia arguta* significantly decreased dermatitis severity and scratching tendency in NC mice through reducing plasma level of selective T₃/2 cytokines, IgE, IgG₁ and IL-4 (Park et al., 2005; Park et al., 2007).

**Amorphophallus konjac**

*Amorphophallus konjac* commonly named Konjac (Family: Araceae) is a plant found in eastern Asia which has an edible corm and is commonly used in Japan as cooking supplement. Konjac Glucomannan, a dietary fiber isolated from the tubers of *Amorphophallus konjac*, is a highly viscous polysaccharide composed of glucose and mannose residues. Consuming Konjac Glucomannan by NC/Nga mouse model reduced the severity of skin symptoms including scratching behavior, suppressed IgE production and substance-p expression and decreased total Immunoglobulin, as well as markedly reduced skin inflammatory immune response related to IL-4, IL-10, TNF-α, and IFN-γ (Onishi et al., 2004; Onishi et al., 2005; Onishi et al., 2007).

**Angelica sinensis**

*Angelica sinensis* (Oliv.) Diels commonly known as Dong quai (Family: Apiaceae) is an herb indigenous to eastern Asia. The topical application of Dong quai to mice with atopic dermatitis inhibited progression of scratching behavior and substance-p expression as wells as reduced the number of mast cells, and the level of serum IgE. Moreover, it reduced the level of cytokines (IL-4, IL-6, TNF-α, and IFN-γ) as well as the expressions of NF-κB in the dorsal skin (Lee et al., 2016).

**Avena sativa**

*Avena sativa* L. with the common name of Oat (Family: Poaceae) is a light-green annual grass originated in European regions, and are now cultivated worldwide (Fleming, 2000). In a controlled clinical study, administration of a body lotion containing colloidal oatmeal (oat flour), oat extract, oat oil and a skin protectant to extra-dry, itchy skin demonstrated significant improvement in alleviating itch (Nebus et al., 2006). In another study involved 29 women with moderate or severe dry skin on their lower legs, associated with chronic mild or moderate itching. substantial improvement in dryness and itching was reported after topical administration of colloidal oat meal (Nebus & Wallo, 2008). Colloidal oatmeal extracts reduced pro-inflammatory cytokines in vitro (Reynertson et al., 2015). In a study, topical application of avenanthramides, a group of phenolic alkaloids present in Oat, reduced pruritogen-induced scratching in a murine itch model (Sur et al., 2008).

**Betula platyphylla**

*Betula platyphylla* Sukat. var. *japonica* Hara commonly named Asian white birch (Family: Betulaceae) is a thin-leaved deciduous hard-wood tree which grows in Korea and Japan. The bark of Asian white birch has been used in Eastern countries for the treatment of a variety of inflammatory disorders including atopic dermatitis (Alakurtti et al., 2006). Oral administration of Asian white birch extract significantly suppressed scratching behavior and skin inflammation through decreasing IgE and IL-4 messenger ribonucleic acid (mRNA) serum levels in mice model of atopic dermatitis, suggesting that it suppresses the T₃/2 cellular response (Kim et al., 2008).

**Borago officinalis**

*Borago officinalis* L. with the common name of Borage (Family: Boraginaceae) is an annual, succulent, bristly-haired herb which is found all over Europe and the USA (Fleming, 2000). In a double-blind, placebo-controlled study, Borage oil-coated undershirts were given to 32 children with atopic dermatitis. After 2 weeks, a marked improvement was demonstrated in symptoms of itch and erythema (Kanehara et al., 2007). The results of a clinical study demonstrated that modest doses of GLA (γ-linolenic acid) produced clinical improvement in the symptoms of atopic dermatitis disease, particularly in itching (Stewart et al., 1991). Borage oil contains a high content (24%) of γ-linolenic acid (GLA) which possessing remarkable anti-inflammatory activity (Horrobin, 2000).

**Bulgaria inquinans**

*Bulgaria inquinans* (Pers.) Fr. commonly known as Black bulgar (Family: Bulgariaceae) is a wood-inhibiting ascomycete growing on freshly felled oak and widely distributed in Northeastern China. The ethanol extract of Black bulgar dose-dependently inhibited scratching behavior induced by compound 48/80 and serotonin in ICR mice and also showed a powerful inhibitory effect on histamine release induced by compound 48/80 (Jiang et al., 2005).

**Cannabis spp.**

*Cannabis* spp. with the common name of Hemp (Family: Cannabaceae) are annual or biennial plants
originated in the Middle East and now grow worldwide in temperate and tropical regions (Fleming, 2000). Cannabis spp. contain several bioactive constituents known as cannabinoids. The best known are tetrahydrocannabinol (THC), cannabidiol and cannabinoil. These compounds affect the itch pathway through cannabinoid receptors (van der Stelt et al., 2005). In humans, topical cannabinoid agonists attenuated histaminergic itch (Karsak et al., 2007) and uremic pruritus (Szepeitowski et al., 2005). Systemic cannabinoids in the form of dronabinol have shown promising effects in management of cholestatic pruritus (Neff et al., 2002). In a study, endogenous cannabinoids downregulated mast cell activation (Facci et al., 1995; Ständer et al., 2008).

**Capsicum frutescens**

Capsicum frutescens L. with the common name of Chile pepper (Family: Solanaceae) is an annual (perennial in the tropics) plant indigenous to Central America and is cultivated today in warmer regions of the world (Fleming, 2000). In a study, topical capsaicin 0.05% liniment showed some anti-pruritic potency in hemodialysis patients with pruritus. Itching, however, was significantly lowered in capsaicin-pretreated patients compared to controls (Weisshaar et al., 2003). In another study, uremic pruritus was successfully treated with capsaicin (Nees et al., 2000). Two trials showed that topical administration of 0.025% capsaicin cream for 6 weeks is effective in treating psoriasis. The first study showed a significant decrease in scaling and erythema in 44 patients with moderate and severe psoriasis (Bernstein et al., 1986). The second was a randomized, vehicle-controlled, double-blind study on 197 psoriasis patients and demonstrated significant decrease in scaling, thickness, erythema, and pruritus (Ellis et al., 1993). In a double-blind study, capsaicin inhibited substance P, a peptide transmitter involved in pain transmission, cutaneous vasodilation, and the inflammatory process (Ellis et al., 1993). Capsaicin produced a hot sensation when applied to the skin which confers its anti-pruritic effects, activating Transient Receptor Potential Vanilloid 1 (TRPV1) which is the key in the various itch pathways (Wilson & Bautista, 2014). Capsaicin should not be used for the treatment of the pruritus on face. It is contraindicated on injured skin (Ellis et al., 1993).

**Centella asiatica**

Centella asiatica (L.) Urban commonly named Centella or Gotu Kola (Family: Apiaceae) is a plant indigenous to southeast Asia and some regions of Africa and America (Fleming, 2000). In a study, anti-pruritic and anti-inflammatory effect of Centella extract in rats were investigated. Oral administration of Centella extract exhibited anti-pruritic activities (George et al., 2009).

**Cinnamomum camphora**

Cinnamomum camphora (L.) J. Presl. commonly known as Camphor tree, Camphor wood or Camphor laurel (Family: Lauraceae) is an evergreen tree indigenous to Vietnam and an extending from southern China to southern Japan (Fleming, 2000). Camphor is a terpene derived from distilling the wood of the Camphor tree which is topically used as analgesic and anti-pruritic agent. It affects itch sensation by activating and desensitizing the Transient Receptor Potential channel (TRP) V1 and A1 in vitro and in rats (Xu et al., 2005; Marsakova et al., 2012). This family of thermosensitive receptor channels is essential in itch perception. Substances with anti-pruritic activity that produce a heating or cooling effect on the skin seem to work at these receptors (Haught et al., 2008). In a study, patients reported that vaporizing the rub - containing menthol, camphor, and eucalyptus - had an effective anti-pruritic activity in epidermolysis bullosa. Furthermore, camphor together with menthol successfully treated hydroxyethyl starch-induced pruritus in one patient (Haught et al., 2008).

**Curcuma longa**

Curcuma longa L. with the common name of Turmeric (Family: Zingiberaceae) is a perennial plant indigenous to India and now is cultivated in tropical regions of Southeast Asia (Fleming, 2000). Turmeric has been used topically to treat a variety of dermatologic conditions due to its antimicrobial and anti-inflammatory properties (Luthra et al., 2001; Velayudhan et al., 2012; Prasad, 2013; Prasad et al., 2014). In a double-blind placebo-controlled trial, significant reduction of pruritus scores was demonstrated in patients with uremic pruritus. Orally prescribed turmeric reduced high-sensitivity C-reactive protein (hs-CRP) levels with no side effect (Pakfetrat et al., 2014). In a randomized controlled trial, curcumin, the major bioactive constituent of turmeric, improved itch and decreased hs-CRP and IL-8 levels in patients with chronic pruritus due to...
sulfur mustard exposure (Panahi et al., 2012a; Panahi et al., 2012b). In psoriasis, oral curcumin together with topical corticosteroids produced greater reduction of disease burden and IL-22 level compared to topical corticosteroids alone (Antiga et al., 2015).

**Diospyros kaki**
*Diospyros kaki* Thunberg, commonly named Persimmon (Family: Ebenaceae) is a tree similar in shape to an apple tree, native to China, Korea, and Japan. The fruit is sweet, slightly tangy with a soft or fibrous texture (Fewtrell & Gomperts, 1977). In a study, it induced a significant alleviation of dermatitis, scratching behavior through reducing the serum level of IgE in atopic dermatitis mice model (Kotani et al., 2000). A flavonol compound, kaempferol, which has been identified in the hot water extract of persimmon leaves, has been reported to inhibit antigen-induced histamine secretion from rat mast cells (Fewtrell & Gomperts, 1977; Chakravarty, 1980; Amellal et al., 1985).

**Fumaria spp.**
*Fumaria* spp. include *F.officinalis* L., *F.vaillantii* Loisel (syn: *Fumaria indica*), *F.parviflora* L. with the common name of Fumitory (Family: Fumariaceae; Papaveraceae) are herbaceous annual flowering plants, which grow in various parts of the world. The aerial part of Fumitory due to its chemical content including benzylisoquinoline alkaloids, flavonoids and organic acids especially fumaric acid have been used for the treatment of pruritus. *F. parviflora* (FP) significantly decreased the severity of uremic pruritus (UP) in hemodialysis patients. The maximum effect of FP was recorded after week 4. This study demonstrated significant decrease in IFN-γ level in patients who received FP compared to those who received placebo (Akrami et al., 2017). The results of clinical trial comparing the efficacy and safety of *F. vaillantii* with cetirizine showed no significant difference in Urtcaria Acitivity Score (UAS) and Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) between two groups of patients after 4 weeks of treatment; however Follow up of patients one month after discontinuation of treatment demonstrated significant reduction of UAS as well as better quality of life score in Fumaria group compared to Cetirizine. About adverse events, the incidence of somnolence in the Fumaria group was significantly lower than in the Cetirizine group (Eghbalian et al., 2018). In a randomized double-blind placebo controlled clinical trial, alcoholic *F. parviflora* extract produced improvement in all types of hand eczema in patients compared to placebo (Jowkar et al., 2011). In a study, it was demonstrated that fumaric acid esters (FAEs) mainly monomethyl fumarate (MMF) present in Fumitory had immunomodulatory, anti-inflammatory, and antioxidative effects and could inhibit proinflammatory activity of human C-reactive protein (CRP) in rats. In an *in vitro* study MMF lowered IFN-γ plasma level (de Jong et al., 1996). In an *in vitro* study, it was demonstrated that psoriasis can be treated successfully with FAEs through reducing production of IFN-γ (Litjens et al., 2004).

**Glycyrrhiza glabra**
*Glycyrrhiza glabra* L. commonly known as Liquorice or Licorice (Family: Fabaceae) is an herbaceous perennial plant indigenous to southern Europe and southwest Asia and now is found in different regions (Fleming, 2000). In a double-blind, vehicle-controlled phase II trial, a standardized extract of Licorice in the form of 1% and 2% gels were used for treatment of AD (30 patients in each group). The 2% licorice gel was more effective than 1% gel and the vehicle in reducing the symptoms of erythema, edema, and itching after two weeks of treatment (Saeedi et al., 2003). In a study, glycyrrhizin inhibited prostaglandin E2 production by activated peritoneal macrophages from rats (Ohuchi et al., 1981).

**Impatiens balsamina**
*Impatiens balsamina* L. commonly named Garden balsam, Garden jewelweed or touch-me-not (Family: Balsaminaceae) is a glabrous, fleshy annual plant grows mostly in the mountainous and tropical regions of Asia and Africa (Fleming, 2000). The effects of hydroethanolic extract from the petals of Garden balsam and its bioactive compounds were examined on chronic and serious pruritus of NC mice with established dermatitis. The extract significantly inhibited serious scratching behavior when administered i.v. 1 h before, or p.o. 24 h before the measurement. Kaempferol 3-rutinoside and 2-hydroxy-1,4-naphthoquinone (lawson) isolated from Garden balsam also inhibited scratching behavior in the NC mouse with established dermatitis. Protective role of Garden balsam extract against scratching behavior when administered orally to 4-week-old NC mice with no symptoms until 13 weeks of age was also reported (Oku & Ishiguro, 2001). Kaempferol
and Kaempferol-3-glucoside (astragalin) from the white petals of Garden balsam exhibited anti-pruritic effect on dextran T40-evoked scratching behavior in mice (Ishiguro & Oku, 1997).

**Lecythis pisonis**

Lecythis pisonis Camb. with the common name of Sapucaia (Family: Lecythidaceae) is a large tree widely distributed in the Amazon region. Leaves of Sapucaia have been used for the treatment of pruritus. Pretreatment of mice with ethanol extract of Sapucaia markedly inhibited scratching behavior induced by compound 48/80. Pentacyclic triterpenes including ursolic and oleanolic acids seems to play the major role in anti-pruritic activity of Sapucaia. Anti-pruritic activity of this herb was through its stabilizing action on mast cell membrane (Saeedi et al., 2003).

**Matricaria chamomilla**

Matricaria chamomilla L. (syn: Matricaria recutita L.) commonly known as Chamomile (Family: Asteraceae) is an annual plant indigenous to Europe and northwest Asia (Fleming, 2000). Different studies have demonstrated that chamomile relieved histaminergic pruritus (Kobayashi et al., 2003; Kobayashi et al., 2005; Chandrashekhar et al., 2011) and inhibited anaphylaxis in type I hypersensitivity allergy models in mice (Chandrashekhar et al., 2011).

Chamomile significantly reduced scratching behavior induced by compound 48/80 and the effect was more distinct when chamomile was given concomitantly with a first-generation antihistamine. In a mouse model of atopic dermatitis, topical application of chamomile reduced scratching behavior and serum IgE level (Lee et al., 2010). Apigenin, one of the major components of Chamomile, reduced NF-κB and IL-4 expressions as well as IgE serum level in mice. Bisabolol, another active compound of chamomile, has been demonstrated to inhibit activation of inflammatory markers including NF-κB, TNF-α and IL-6 in murine models (Kim et al., 2011; Maurya et al., 2014).

**Mentha x piperita**

Mentha x piperita L. (syn: Mentha balsamea Wild.) commonly known as Peppermint (Family: Labiatae; Lamiaceae) is a perennial plant indigenous to Europe and the Middle East. The plant has widely spread and cultivated in many regions of the world (Patel et al., 2007). In a randomized triple-blind clinical trial, external use of Peppermint oil twice a day during two weeks, significantly decreased the severity of skin itching in pregnant women with pruritus gravidarum compared to placebo group (Akhavan-Amjadi et al., 2012). Topical application of peppermint oil created a cooling sensation and activated the thermosensitive TRPM8 and TRPA1, which resulted in inhibited itch signal transmission (Fröhlich et al., 2009). Relieving effect on pruritus has been demonstrated under conditions including lichen amyloidosis and epidermolysis bullosa (Fröhlich et al., 2009; Danial et al., 2015). Active component of Peppermint is menthol, a cyclic terpene alcohol that is responsible for characteristic smell of Mentha genus (Jonathan et al., 2013). In a study, the mixture of 1% phenol and 1% menthol significantly alleviated mustard gas-induced pruritus in chemical warfare-injured patients compared to placebo (Panahi et al., 2007). Moreover, a topical lotion containing 0.5% menthol and 0.5% camphor was beneficial in mustard gas-induced pruritus. It caused a rapid relief of the symptoms during attacks and decreased the frequency of attacks with topical application oof 3 times daily (Haught et al., 2008).

**Oenothera biennis**

Oenothera biennis L. commonly known as Evening primrose or Evening star (Family: Onagraceae) is a biennial plant originally indigenous to North America and is now naturalized throughout most of Europe and parts of Asia (Fleming, 2000). The oil extracted from seeds is rich in poly unsaturated fatty acids especially γ-linolenic acid (GLA). In a double-blind study, 9 and 7 dialysis patients were randomly assigned to receive either Evening primrose oil (EPO) or linoleic acid (LA) (2 g per day) for 6 weeks and the symptom of pruritus were assessed by questionnaire. The patients given EPO exhibited a significant increase in plasma dihomo-γ-linolenic acid. They also showed a significant improvement in pruritus than those given LA (Yoshimoto-Furui et al., 1999). A meta-analysis of 26 clinical studies including 1207 patients indicated that Evening primrose oil has a beneficial effect on pruritus that becomes apparent between 4 and 8 weeks after beginning of treatment (Morse & Clough, 2006).

**Panax ginseng**

Panax ginseng C.A. MEYER with common name of Ginseng (Family: Araliaceae) is a perennial plant indigenous to China and is now cultivated in eastern Asia and Russia (Fleming, 2000). The roots are the medicinal part of the plant and usually harvested when it is five or six years old. Ginsenosides are
triterpene saponins of the root with various biological activities, including anti-allergic activity (Choo et al., 2003; Park et al., 2003). The anti-allergic activity of ginsenosides is due to compound K produced during the biotransformation of ginsenosides by human intestinal microflora. Ginsenoside Rb1, a triterpene saponin isolated from Ginseng, ameliorated scratching behavior induced by compound 48/80 in ICR mice (Shin & Kim, 2005). In a study, Korean Red Ginseng (KRG) and ginsenosides exhibited anti-inflammatory and anti-allergic effects against atopic dermatitis by inhibiting Th2 mediated inflammation as well as by diminishing the itching sensation (Lee & Cho, 2017).

**Platycodon grandiflorum**

*Platycodon grandiflorum* (grandiflorus) Jacq. A. DC. commonly known as Platycodon, Balloonflower, or Chinese bellflower (Family: Campanulaceae) is a perennial plant indigenous to eastern Asia and Siberia (Fleming, 2000). The fermented extract of Platycodon Markedly reduced the serum level of IgE and its anti-scratching behavioral effect was more potent than Platycodon extract. This result indicated that anti-pruritic effect of Platycodon was enhanced by fermentation (with Saccharomyces cerevisae) (Ha et al., 2014).

**Quercus acutissima**

*Quercus acutissima* Carruth. commonly known as Sawtooth oak (Family: Fagaceae) is an Asian species of Oak tree native to China, Korea, Japan, Indochina and the Himalayas. Methanolic extracts of the plant bark showed anti-pruritic activity in cutaneous diseases induced by substance P in mice. When administered orally 30 min before SP injection, the methanol extract inhibited SP-induced itch-scratch response without affecting locomotor activity (Tohda et al., 2000).

**Rumex Japonicus**

*Rumex Japonicus* Houtt. with the common name of Goat-hoof, or Japanese Dock (Family: Polygonaceae) is a perennial herb native to Eastern Asian countries. Administration of Goat-hoof in NC/Nga mice for 42 days caused remarkable reduction in scratching behavior and IgE and IL-4 serum levels (Lee et al., 2006).

**Saururus chinensis**

*Saururus chinensis* (Lour.) Baill. commonly named Saururus (Family: Saururaceae) is a perennial plant native to Korea. Oral administration of Saururus leaf extract to NC/Nga mice for 8 weeks markedly suppressed development of AD-like skin lesions and reduced scratching behavior and IgE serum level. These results modulating the T_h1/T_h2 serum level by Saururus (Choi et al., 2008).

**Vaccinium myrtillus**

*Vaccinium myrtillus* L. with the common name of Bilberry (Family: Ericaceae) is a deciduous, dwarf shrub common to central and northern Europe, Asia and North America (Fleming, 2000). Three weeks oral administration of Bilberry extract alleviated pruritus and scratching behavior in a mouse model of chronic allergic contact dermatitis (Yamaura et al., 2011). Moreover, anthocyanin-rich Bilberry extract alleviated pruritus, suggesting that the anthocyanins are the main active components. The inhibitory effect of Bilberry anthocyanins on chronic pruritus of experimental dermatitis might be through inhibition of mast cell degranulation (Yamaura et al., 2012).

**Vanillosmopsis arborea**

*Vanillosmopsis arborea* Baker commonly known as Candeeiro (Family: Asteraceae) is a small tree grows in Brazil. Its wood has a strong odor of chamomile and burns easily with a strong flame (Matos et al., 1988). Essential oil of Candeeiro, which is rich in (−)-α-bisabolol (a sesquiterpene alcohol), inhibited histamine-induced scratching behavior immediately after application in histamine-induced mice model of pruritus (Campos et al., 2014; da Costa, 2015).

**CONCLUSION**

Itch or pruritus is a distressing and uncomfortable sensation of the skin that provokes the desire to scratch. Pruritus can sometimes be disabling, and extremely difficult to be managed effectively. Despite to various systemic and topical conventional drugs used for management of pruritis, the necessity for identifying more efficacious drugs with lower rate of adverse events is still obvious. Herbal therapy for pruritic diseases has been used for thousands of years. In the present study, we introduced some medicinal plants and their bioactive components for the management of pruritus with the prospect of further investigation on these herbs as promising anti-pruritic agents. Although many herbs are listed in the management of pruritus, few have actually been investigated with well-designed clinical trials.

There were 23 human studies, 32 in vivo and only 6 in vitro studies which considered to be mentioned in this review. Among the human studies, medicinal plants including *Avena sativa, Borago*
officinalis, Capsicum frutescens, Curcuma longa, Fumaria spp., Mentha x piperita and Oenothera biennis showed the best anti-pruritic activity. Among preclinical studies, Actinidia arguta, Amorphophallus konjac, Angelica sinensis, Betula platyphylla, Diospyros kaki, Impatiens balsamina, Lecythis pisonis, Matricaria chamomilla, Platycodon grandiflorum, Rumex Japonicus, Saururus chinensis and Vaccinium myrtillus showed remarkable activity in the management of pruritus.

Among different herbs mentioned in this review, Curcuma longa, and Fumaria spp. had the highest level of clinical evidence for their anti-pruritic effect through different mechanisms.

Bilberry anthocyanins, ginsenosides (triterpenoid saponins), avenanthramides, bradykinase, mannose-6-phosphate, acemannan, lupeol (a sterol), (-)-α-bisabolol, GLA (γ-linolenic acid), cannabinol, cannabidiol, dronabinol, THC (tetrahydrocannabinol), capsaicin, camphor, curcumin, kaempferol, kaempferol 3-rutinoside, Kaempferol-3-glucoside (astragalin), 2-hydroxy-1,4-naphthoquinone (lawson), ursolic acid, oleanolic acid, apigenin, menthol, fumaric acid, MMF (monomethyl fumarate), glycyrrhizin, glycyrrhetinic acid and glycyrrhizin were presented as the main bioactive components of medicinal plants which exhibited anti-pruritic property.

Anti-pruritic activity of the herbs and their bioactive constituents was mediated by different mechanisms including reduction of IgE serum level, suppressing the T2 cellular response, reducing proinflammatory cytokines (IL-4, IL-6, IL-8, IFN-γ, TNF-a), decreasing or suppressing the expression of substance P, reducing the expressions of NF-kB, inhibiting prostaglandin E2 production, activating TRPV1, reducing hs-CRP, activating the thermosensitive TRPM8 and TRPA1, and stabilizing action on mast cell and inhibiting the release of histamine from them.

Result obtained from the clinical trials evaluating anti-pruritic effects of the herbs and their bioactive constituents, showed that there is a need for conducting further well-designed human studies with larger sample size and longer follow-up period to confirm the efficacy of medicinal plants and their bioactive components in the management of pruritus.

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