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**Review Article** 

# CLINICAL REVIEW: URTICARIA – ITCHSAL, RADION & BHUNIMBADI KWATH – A

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# ABSTRACT

Urticaria, also known as hives among people, is a very common disease characterized by erythematous, oedematous, itchy, and transient plaques that involve skin and mucous membranes. It is classified as acute spontaneous urticaria, chronic spontaneous urticaria, chronic inducible urticaria, and episodic chronic urticaria. Many factors such as infections, medicines, food, psychogenic factors, and respiratory allergens are accused of aetiology, but sometimes, it is idiopathic. Clinical presentation involves red, swelling, and itchy plaques. The lesions usually resolve spontaneously within 2-3 h without a trace. The patients are sometimes confronted with an angioedema that can also involve the respiratory tract. In this case mucous membranes, such as eyelids, lips, swell with some pain and burning sensation. If respiratory tracts are involved, it may be life threatening and should be treated urgently. The diagnosis is usually straightforward, urticarial vasculitis, drug eruptions, viral eruptions, and urticaria pigmentosa must also be considered. H1 antihistamines and, sometimes, short-term systemic corticosteroids are preferred for the treatment; H2 antagonists may be added during resistant cases, although other treatment options, such as omalizumab, cyclosporine, and leukotriene receptor antagonists, may be considered during missed events.

Keywords: Angioedema, treatment, urticaria

Urticaria is a disease characterized by erythematous, oedematous, itchy and transient urticarial plaques, and covering the skin and mucous membranes. Also known as hives among people. It is a very common entity. 8.8–20% of individuals in the community experience an attack of urticaria at least once in their lifetime [1]. It can be seen in all ages and sexes but is slightly more common in young adults. In 40–50% of the patients, urticaria and angioedema are seen in combination, only urticaria or angioedema is seen in 40% and 20% of the people, respectively [2].

# Classification (Table 1)

Acute spontaneous urticaria	It lasts <6 weeks $[\underline{3}]$ .
Chronic spontaneous urticaria (CSU)	It recurs at least twice a week and lasts $>6$ weeks [3].
Physical urticaria (chronic inducible urticaria)	It emerges due to etiological factors as dermographism, cold, hot, vibration, pressure, and solar factors. It constitutes 20–30% of chronic urticaria [4].
Episodic chronic urticaria	It lasts >6 weeks but recurs <2 times per week [5].

It should be kept in mind that CSU and physical urticaria can be seen together. CSU is most commonly associated with dermatographia urticaria and late pressure urticaria [2].

## Pathogenesis

The main mechanism in the formation of urticaria is the release of various mediators from mast cells. Type 1 immunoglobulin (Ig) E-dependent hypersensitivity reaction is seen in acute urticaria. The antigen entering the body binds to specific antibodies on mast cells and basophils, causing the release of many mediators, primarily histamine. As a result, eldema due to erythema and increased permeability secondary to vasodilatation [6]. Mast cells cannot be restimulated until regranulation after degranulation, which explains why the urticaria plate does not reappear for several days on the region.

In chronic urticaria, the antigen entering the body binds to the IgE high affinity (Fc $\epsilon$ RI $\alpha$ ) Fc receptor located on the mast cells and circulating basophils in the skin and degranulation from these cells occurs. When the same antigen is encountered for the 2<sup>nd</sup> time, these IgE antibodies that are already present on the mast cells and basophils immediately bind to the antigen and develop an allergic reaction more quickly [7]. This shows us that autoimmunity is also important in chronic urticaria.

#### Etiology

Many factors may be responsible in the etiology of the disease. Often, encountered factors include:

- Medications: Any drug may cause urticaria. However, the most commonly encountered ones are penicillin, aspirin, nonsteroidal anti-inflammatory drugs, sulfonamides, thiazide diuretics, oral contraceptives, angiotensin-converting enzyme inhibitors, vitamins, codeine, morphine, curare and its derivatives, synthetic adrenocorticotropic hormone, and radiocontrast substances. It may manifest from 1–2 h to 15 days after oral intake. Urticaria related to the drugs given intravenously will occur immediately. While the drugs generally cause acute urticaria, they may cause emergence or exacerbation of CSU [8].
- 2. Foods: Foods often encountered as causes of urticaria include nuts, eggs, fish, seafood, chocolate, meat, cow's milk, fruits (citrus fruits, grapes, plums, pineapples, bananas, apples, and strawberries), vegetables (tomatoes, garlic, onions, peas, beans, and carrots), mushrooms, fermented foods, spices, and spirits. Preservatives such as azo dyes, benzoic acid derivatives, and salicylates and food dyes are also important causative factors. Urticaria is usually seen 1–2 h after ingestion. Food-related urticarial rashes are more common in children [9]. Although it is accepted that foods have a place in the etiology of acute urticaria, their roles in the etiology of CSU have been not proven yet. It is thought that mostly pseudoallergens are involved in CSU, and therefore, diet is recommended for these patients [10].
- 3. Respiratory allergens: Pollen, mold spores, mites, animal dandruff, and hairs may cause urticaria when taken through the respiratory tract [11]. Smoking is also an important factor since it contains many chemicals and can worsen the urticaria, hives should be advised to stop smoking. Urticaria caused by respiratory allergens usually occurs immediately after contact.
- Infections: Respiratory infections such as sinusitis, tonsillitis, dental abscesses, urinary tract infections, hepatitis, infectious mononucleosis, and parasites may cause urticaria [12]. Parasitoses are the cause of urticaria, especially in children.
- 5. Contact urticaria: Latex, cosmetics, and chemicals may cause urticaria by contact [13].
- 6. Insect bites: They should be questioned, especially in children  $[\underline{14}]$ .
- 7. Psychogenic factors: Reasons such as stress, sadness, and depression may aggravate the preexisting urticaria and also induce urticaria [15].
- 8. Systemic diseases: They may cause especially chronic urticaria. The presence of thyroid diseases and rheumatic diseases such as systemic lupus erythematosus, lymphoma, leukemia, and carcinomas may be investigated as required. It should be noted that urticaria may occur also in pregnant women [11].

- 9. Physical factors: Urticaria may develop due to external factors such as pressure, hot, cold, and dermographism [13]. Urticaria secondary to pressure generally manifests an average of 3–4 h after exposure to pressure. Therefore, they are termed as delayed pressure urticaria.
- 10. Hereditary: Hereditary urticaria is seen in types of urticaria as angioedema and familial cold urticaria.
- 11. Idiopathic urticaria without any known cause may be also seen.

#### **Clinical Manifestations**

The urticarial plaque has three characteristics as characteristic redness, blistering, and itching. Sometimes, a burning sensation may accompany. Lesions can occur anywhere in the body and recover in approximately 2–3 h without leaving a trace. This spontaneous recovery can sometimes last up to 1 day.

In angioedema, especially in areas such as eyelid and lip mucosae, there is a sudden-onset skin swelling. Pain and burning sensation may be at the forefront rather than pruritus. The lesions regress spontaneously in about 72 h [16].

Dermographism is an erythema and edema occurring about 10–20 min after applying mechanical trauma to the skin. While this situation may be encountered in almost half of the population, if this region is itchy, then this entity is called dermatographic urticaria. This condition is seen in about 4% of the society [13].

#### **Diagnosis and Differential Diagnosis**

It is quite easy to diagnose based on clinical appearance and anamnesis. However, it is also sometimes confused with drug eruptions, viral rashes, connective tissue diseases, photosensitive diseases, urticaria pigmentosa, urticarial vasculitis, and a number of syndromic diseases [17].

It is very important to obtain detailed anamnesis from the urticaria patient to reach the etiology. The patient should be asked about the time of onset, development, localization of lesions, systemic complaints, food intake, stress, and regular or occasional medication use. There is no need for routine laboratory tests and allergy tests in acute urticaria. In a guideline published in the United States, it has been reported that if there is no evidence to support a diagnosis, then there is no need for laboratory examinations [3]. Just 25% of acute urticaria cases become chronic in time [18].

#### **Treatment: Basic steps in the treatment**

Elimination of detectable etiologic causes and avoiding triggers constitute the first step of treatment. If the patient expresses that the lesions occur in any condition, such as after a drug or food intake, he must avoid this situation. If there is a noticeable infectious condition, it should be treated.

In an important subgroup of patients with chronic urticaria, exacerbations triggered by physical stimuli occur. Training patients can help them avoid these stimuli or understand their symptoms. As an example, heat (hot showers and excessive humidity) is the common trigger of many people. Tight clothing or rubber

bands may exacerbate symptoms. On the other hand, physical urticaria (dermographism, cold, hot, solar, cholinergic, pressure urticaria, etc.) developed with the stimuli of physical factors should be properly diagnosed and the stimulant should be eliminated.

Many drugs, especially aspirin and nonsteroidal anti-inflammatory drugs, may worsen symptoms. It is best to stay away from these drugs during this period [19].

A 4-week elimination diet is recommended for pseudoallergens thought to induce urticaria. Alcohol consumption is not recommended [20].

Concomitant stress, sleep disturbance, infections, premenstruation, and irregular antihistamine use may also aggravate the disease [15].

Rarely reported triggers are cigarette smoke, house dust mites, pollens, molds, and spores, and the patient should be informed about all these possible irritants [11].

After warning the patient about these issues, it is necessary to control the symptoms by suppressing the mediator release as the second step of the treatment.

In the treatment of urticaria (with or without angioedema), the focus should be on the immediate relief of pruritus and angioedema, if any. Approximately two-thirds of the cases of acute urticaria may be spontaneously confined and recover spontaneously.

*Sutshekhar Ras* is a very commonly used drug in *Amlapitta* and it helps not only in reducing the symptoms but also maintains the health. The specially prepared lifestyle chart containing *Ahara* and *Vihara* helps in reducing the symptoms and maintaining the healthy lifestyle. This drug is very beneficial in this disease due to multiple actions such as anticholinergic and directly acting ANTACIDS.

Most of the drugs of *Sutshekhar Rasa* are *Tikta, Kasaya* and *Madhur Rasa Pradhana* properties. *Madhur Tikta, Kasaya Rasa* are *Pitat Shamaka. Tikta* and *Kasaya Ras* also subside *Kapha Doshas. Madhura Rasa* counteracts the *Tikshan Guna* of vitiated pitta causing soothing effect, promotes strength and pacify *Vata Pitta Doshas* and also relieves *Daha* (burning sensation). In *Amalpitta, Mandagni* leads to *Ama* formation. *Pippali* is the best medicine for *Ama Pachana*. All the drugs are having *Deepan Pachan* properties which improve the status of *Agni. Sankh Bhasama* and tankan both having *Kshariya* nature which reduces the *Amlitya* (acidic nature) thus neutralize the acidity and maintains acid base balance in stomach. In Ras Taringini it is clearly mentioned that they both cures *Amalpitta* and are *Agnivardhak* in nature. According to Ayurveda Prakash *Tamra Bhasma* is also mentioned as *Amalpittnashak. Laghu Sutshekhar Ras* also has same benefits like *Sutshekhar Ras* and has a detoxifier and digestive affect same as that of *Sutshekhar Rasa*.

## **BIOLOGICAL AND PHARMACOLOGICAL ACTIONS:**

*Alpinia galanga* has currently become a popular herbal plant for research, so *Alpinia galanga* has been studied for its pharmacological effects. Some of the health benefits of *Alpinia galanga* are described below.

Antimicrobial Activity The extracts from Alpinia galanga have shown significant results in inhibiting the growth of Escherichia coli, Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa, and Klebsiella pneumonia, but are not effective in inhibiting bacteria such as Staphylococcus epidermidi [57]. Essential oil compounds in the galangal rhizome have significant activity in inhibiting the growth of bacteria such as Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Streptococcus suis, Pasteurella multocida, Arcanobacterium pyogenes, and Erysipelothrix rhusiopathiac. The effect is associated with bisase, 4-ally phenylacetate, and 1,8- cineole [58]. While the results of ethanol extraction from galangal flowers have shown significant effects in inhibiting Staphylococcus aureus, seen in the diffusion tests or minimum inhibitory concentrations (MIC) of galangal flower extracts as 0.352–0.547 mg/ml and inhibition zones around 26–31 mm, the ethanol extracts from galangal flowers have not shown significant results in inhibiting the growth of Salmonella bacteria and Escherichia coli [59]. The ethanol extract of Alpinia galanga significantly inhibited the bacterium, Staphylococcus aureus. Using the diffusion test or MIC (minimum inhibitory concentration), the galangal rhizome extract MIC was 0.325 mg/ml and MBC (the minimum bactericidal concentration) was 1.3 mg/ml. Observations using electron microscopy showed that the galangal rhizome extracts cause damage to the outer and inner membranes of bacteria, and there is cytoplasmic coagulation. Nucleic acid damage results from the removal of cell material from the cytoplasmic by coagulation activity [60]. Alpinia galanga is has antifungal activity and can replace antifungal products such as Ketoconazole and Amphotericin B [61]. Alpinia galanga is is effective in inhibiting the growth of yeast such as Candida albicans [62]. The ethanol extracts of Alpinia galanga have phytotoxic effects against Lemna minor and have antifungal effects on the growth of the fungus, Trichophyton longifusus [63]. Alpinia galanga ethanolic extracts at a concentration of 10 mg/ml are also able to inhibit the growth of the phytopathogenic fungi, *Candida albicans, Fusariumoxy sporum*, and *Colletotric* hummusae [64]. Methanol extracts of Alpinia galanga inhibited the development of human cytomegalovirus and human immunodeficiency virus type 1. Chloroform extracts of Alpinia galanga at a concentration of 1 µg/ml showed inhibition of the growth of Entamoeba histolytica. Extraction galangal rhizome also inhibits the growth of Giardia intestinalis at MIC (minimum inhibitory concentration) of 125 µg/ml [65, 66]. extraction of the galangal rhizome using chloroform, ethyl acetate and hexane showed inhibition of the growth of promastigote, L. donovani in vitro [67]. Antifungal Activity Ethanolic extracts from Alpinia galanga have antifungal activity, showing significant results in inhibiting the growth of the fungus, Trichophyton longifusus [63]. Diterpen compounds in Alpinia galanga (E), such as -8β, 17-epoxylabd-12ene-15, and 16-dial synergistically play important roles in the antifungal activities of chalcones and quercetins against the growth of Candida albicans [68]. A high antifungal activity of DCM and n-hexane extracts of Alpinia galanga have been observed using diffusion tests or inhibition zone tests. Alpinia galanga contains flavonoids and phenolic compounds, which also play roles in counteracting free radicals inhibiting the release of betahexominidase, and also play a role in RBL-2H3 cells, which can act as a marker for degranulation by antigen mediation [70]. The galangal rhizome has anti-inflammatory potential, and total aqueous extracts (TAQs) and total alcoholic extracts (TAEs) evaluations have been conducted on the galangal rhizome. The anti-inflammatory properties of a TAQ extract of galangal and TAE from galangal rhizomes were evaluated in sub-acute (M2; cotton-pellet-induced granuloma) and acute (M1; carrageenaninduced paw edema) rat models [71]. Analgesic and anti-inflammatory activities of the galangal rhizomes extract have been shown with topical preparations. Evaluation of anti-inflammatory activity has been reported against carrageenan-induced edema in experimental rats and in formalin tests. Methyl salicylate ointment and piroxicam gel have been studied as positive controls for analgesic and anti-inflammatory activities. The rate of edema inhibition with preparations containing extracts at 1-5% w/w showed significant results that varied from controls. The anti-inflammatory effect of SN at a dose of 4-5% is in accordance with the effect of Piroxicam after 3 hours of carrageenan injection [72]. Antiinflammatory and anti-diabetic activities have been reported for methanolic and phenolic extracts from the galangal rhizomes [73]. The effect of p hydroxycinnamaldehyde from Alpinia galanga acetate extract has been reported in cases of chondrocytes in humans. Osteoarthritis is a disease that is often found in humans. Significant side effects occurred in patients who were given nonsteroidal anti-inflammatory therapy [74]. Anti-hepatotoxic Activity Paracetamol hepatotoxicity treatment has been reported in rats using an Alpinia galanga extract. This study was carried out using Alpinia galanga extract at concentrations of 200 and 400 mg/kg in order to detect hepatoprotective effects on hepatotoxicity in rats induced by paracetamol [62]. Antioxidant Activity Alpinia galanga extract has antioxidant activity. A water extract containing 50% ethanol was studied for its antioxidant activity, and its composition compared with Khairullah et al. /A Review of an Important Medicinal Plant: Alpinia galanga (L.) Willd 392 Systematic Reviews in Pharmacy Vol 11, Issue 10, Oct-Nov 2020 two other samples, namely essential oils and water extracts. Antioxidant activity was measured using the oxygen radical absorption capacity (ORAC) and 2,2- diphenyl-1-picrillhidrazil (DPPH). It has been reported that an ethanol extract had the highest free radical DPPH neutralizing ability. The ORAC value of the ethanol extract had the highest value compared to essential oils and water extracts [75]. It has been reported that galangal rhizome has antioxidant activity when extracted with 1- acetoxychavicol acetate and its compounds [76]. A methanol extract from *Alpinia galanga* has has been evaluated for its antioxidant activity (AOA) and total phenolic content using the DPPH test, chelating iron ions, reducing power (RP), and the AOA β-carotene bleaching tests [77]. Immunomodulatory Activity A study on mice reported immunostimulant activity in a solution of polysaccharide extract in warm water from Alpinia galanga [78]. Anti-diabetic Activity The galangal rhizome extracts have shown hypoglycaemic activity on rabbit blood glucose levels [79]. The results of the treatment using galangal rhizome powder, and methanolic and water extracts showed significant results in reducing blood glucose levels in healthy rabbits and improving the rhizome also inhibited the glycosylation of haemoglobin. Galangal rhizome significantly has antidiabetic activity through in vitro, by inhibiting dose dependent  $\alpha$ -amylase and  $\alpha$ -glucosidase activity [81]. Anti-ulcer Activity: An Alpinia galanga ethanolic extract has anti-ulcer, ant gastric secretion, and cytoprotective properties in rats. The galangal rhizome is also widely used to treat stomach disorders. An Alpinia galanga ethanolic extract showed significant results in reducing gastric secretion and was cytoprotective; therefore, Alpinia galanga also had antiulcer activity [82]. It was reported that the galangal rhizome ethanolic extracts caused cytological and biochemical changes in rats induced by cyclophosphamide. The galangal rhizome, in addition to being a spice, is also used in medicine to treat stomach aches, gastralgia, dyspepsia, digestive disorders, sea ailments, tonics, and ulcers [83]. There are also anti-feedants and lethal substances in the galangal rhizome extract. An active compound in the galangal rhizome extract shows insecticidal activity; the compound is acetate 1'-acetoxicaviol, which has the molecular formula: C13H14O4. Some other galangal species also contain compounds that are anti-feedants [84]. Anti-tumor Activity The galangal rhizome contains bisdemethoxycurcumin (BDMC) and 1,7-bis (4-hydroxyphenyl) -1,4,6-heptatrien3-one (BHPHTO) compounds, which were investigated to determine their effectiveness in the human melanoma cell line, A2058, which showed that the compounds inhibited cell proliferation. Furthermore, studies of B16-F10 cells showed reduction of melanin content and inhibition of tyrosinase cellular activity [50]. Antiallergic Activity The galangal rhizome has anti-allergic properties and is an effective allergy treatment. In a rat model, the galangal rhizome active compounds inhibited the release of IgE that was mediated in passive skin anaphylaxis reactions [52]. Anti-HIV Activity The galangal rhizome extract contains the active compound, 1'S-1'acetoxychavicol acetate, which plays an important role in blocking reverse transport replication of anti-human immunodeficiency virus type 1 [85]. Anti-SARS-CoV-2 activity The use of herbal treatments increased rapidly during the 2020 coronavirus pandemic (Covid-19). In Indonesia, each ethnic group has its own medicinal herbs, which are mostly obtained from local plants. Herbal plants in the Zingiberaceae family include Alpinia, Kaemferia, Curcuma, Zingiber, Costus, and Elattaria, which contain compounds often used as herbal treatments [86]. Utomo et al (2020) demonstrated the potential inhibitory effect of Citrus, Curcuma, Caesalpinia, and Alpinia on SARS-CoV-2 infection, so their development may provide novel treatment and prevention strategies for COVID-19 treatment. One of the phytocomponents of Alpinia galanga has been predicted as a possible potent antiviral agent against SARS-CoV-2 [87].

#### Sariva

It is also known as Indian Sarsaparilla, which is highly used to kill the worms present in intestine. In Ayurvedic system, this plant is used in treatments of oligospermia, gastritis, anorexia, and menorrhagia, and worm infection. *Sariba* in Vedic Era (2000 B.C. to 800 B.C.) Ancient literature has many references for *Sariva*. Though *Sariva* is not found in Rig-Veda, Yajurveda, Samveda and Atharvaveda. Atharva-Parishishta described Ananta (1/43/6) and *Sariba* (Hemidesmus indicus R.Br.) (5/1/5); also in Kalpasutra

use of *Sariva* is mentioned three *Sariba* in Samhita: (1) Charaka Samhita Bruhattrayi including Charaka, Sushruta, and Vagbhata all are well known for their creations of corresponding Samhita have mentioned *Sariva* in some of the formulations indicated for preventive and curative purposes. Acharya Charaka described *Sariva* in following six Mahakashaya: Reff.-Cha. Su.4 [1-4]. (1) Varnya Gana, (2) Kanthya Gana, (3) Stanyashodhana Gana, (4) Jvaratisarahara Gana, (5) Purishsangrahniya Gana, and (6) Dahaprashamnan Gana. It is described in 19 formulations in the treatment of Jvaratisara, Kasa, Kushtha, Atisara, Visarpa, Shiroroga, Arsha, Vishachikitsa, and Grahani

Sariva associate Indian medicative plant is found within the land regions up to a height of 1400 m and within the forest areas of Western Ghats. This medicative plant has various common names such as Sariba and Sveta Sariva in Sanskrit, Magali beru and Makali beru in South Dravidian, and Mahali kizhangu in Tamil. The biological science name for this Indian woody plant is Decalepis hamiltonii. Sariba plants square measure the climb woody plant with articulated branches and cylindrical, fleshy and aromatic roots. Leaves of this plant occur in other way and square measure orbicular, elliptic-obovate. This square measure just about 5 cm long; arched and also the main nerves gift in pairs. The flowers of this medicative plant square measure little and whitish-brown in color. The fruits square measure little and bear shortly ovate seeds. Sariva plants square measure necessary for his or her medicative values. The roots of this plant square measure thought of as associate course that square measure used as blood-purifier and have a sweet sarsaparilla-like style. In Ayurvedic medicative plant elements square measure used for the treatment of nephropathy, haemorrhage, gout, wounds, leprosy, anaemia, and jaundice. There is large compilation of Sariva plant. This shows that this herbal drug is used by our ancestor as a medicine. They know how this plant is useful for the various ailment

#### Table 2: Treatment algorithm for urticaria

Start with ItchSAL and Sarivadhyasav

# t

If symptoms persist more than 2 weeks

#### Second-line

Add RadiON Tablet 1-1-1

#### t

If symptoms persist for additional 1-4 weeks

#### **Third-line**

#### Do RaktaMokshan 60ml

## t

If symptoms cannot be controlled, Panchakarma may be used for up to 15 days.

# CONCLUSION

Urticaria is an acute and chronic itchy rash that can be quite irritating. Angioedema may accompany urticaria, and rarely, it may be fatal. Although many etiologic factors such as infections, drugs, and foods are blamed in their etiology, they are often idiopathic. In the treatment of patients, if there is a detectable etiologic or trigger factor, it should be avoided and the patient should be warned for the possible existence of physical urticaria. Although ItchSAL is used in the first step treatment, a wide variety of agents have been used, including *Soot Shekhar Ras* and *Kushthakulinjan*. In medicine, there is no disease, there is a patient, and every patient should be treated with appropriate care. Nevertheless, it should be kept in mind that it is still a challenging disease for both the patient and the physician.

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<u>Go to:</u>

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