



TRADITIONAL AND MEDICINAL USE OF BARBALOIN: POTENTIAL FOR THE MANAGEMENT OF VARIOUS DISEASES

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ABSTRACT

Barbaloin is the phytoconstituent which is obtained from the plant known as *aloe vera*. As we all know *aloe vera* is the main curative medicinal plants, has been traditionally used as alternative treatment against the many skin diseases. Barbaloin extracted from the *aloe vera* plant which is physically light yellow colored powder. Extraction of barbaloin from the plant *Aloe barbadensis Miller* had been accomplished by the Soxhelt extraction, Batch extraction experiment and Ultrasound assisted extraction method (UAE). Barbaloin showed various kinds of therapeutic and medicinal properties like anti-diabetic, antioxidants, anti-cancer, anti-inflammatory and anti-microbial. It also has good effect on cardiovascular system, test perception, enzyme or metabolism and bioavailability. Our Skin plays an important role in the development of skin diseases because there are many types of skin disorders are developed and the variety of disorders may result to dermatitis or they affect the social wellbeing of a person. Due to their good pharmacological activities, Barbaloin have great potential to treat the different type of skin disorders like Eczema, Psoriasis, Burns and wound, Acne, Dandruff, Frostbite, Rashes, Cold sores, Razor burn and Sunburn. To access the effective use of barbaloin there are various attempts have been experimented on the subject of their Pharmacological activities to check their effect on skin disease and the steps regarding the Isolation of barbaloin also has been made. We can examine their effects on chronic skin diseases. In this review article we discuss about the potential of barbaloin on skin disorders, medicinal importance or Pharmacological activities and their methods of extraction.

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INTRODUCTION

The Barbaloin is the natural phytoconstituent of aloe vera (10-beta -D-glucopyranosyl-1, 8-dihydroxy-3-hydroxymethyl-9(10H)-anthracenone) and is the most precise secondary compound of *aloe plant*, due to their ease of availability it is mainly found throughout the world. The main and important quality of Barbaloin is to give the yellow fluorescence. In the study the barbaloin gives us strong action in the inhibition and release of histamine from the mast cells. According to their anti-inflammatory action the barbaloin shows great inflammatory effect as compare to the potent drug, Indomethacin. This study proved that the herbal drug barbaloin show the varieties of active sites at in mast cells. Barbaloin content is more in the younger leaves of the plant as comparison to older leaves of *Aloe vera*. But, the third part of the *aloe vera* leaves show the highest percentages of barbaloin in the leaves [1].

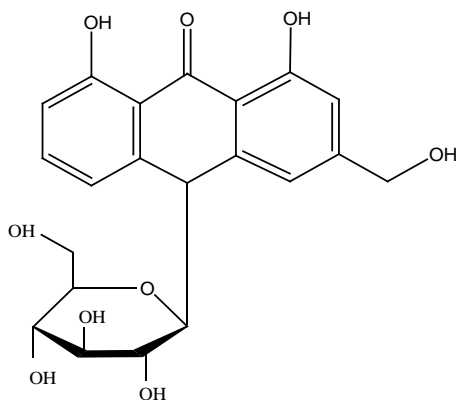


Figure 1 Chemical structure of Barbaloin

Barbaloin is an *aloe emodin* anthrone of C-glucoside and it will occur in the outer layer of the aloe species. A report has been available to show there are upto 30% *aloe* constituents are present in the dried leaf exudates of *aloe plant* and all these phytoconstituent play an major role in the protective mechanisms in front herbivores. There are many attempt have been made regarding the oral administration of barbaloin but there is no proper result shows their better effect. Because in the oral route the barbaloin is poorly absorbed and it is metabolized by intestinal microflora, that is willingly absorbed. Barbaloin is mostly used as cathartics or also it has been used as a bittering agent in the preparation of alcoholic beverages. In the invivo study the Barbaloin shows great anti-inflammatory and cathartic effects. But in case of In vitro studies it is found that it has superior toxicity to carcinoma cells a potent inhibitor on transformation [2].

As we all know *aloe vera* is the effective and miracle plant and barbaloin is the secondary metabolite of this plant. It is one of the effective components with their amazing laxative property that was observed in rats by in vivo study. For the validation and determination of barbaloin there are some methods were made like fluorometry, colorimetry and HPLC [3]. According to Indian system of medicine many plants have been used for their cathartic property in the treatment of stomach constipation, and the plant name as *aloe vera* (Fam. Liliaceae), it is one of the active plants with effectiveness. Commonly it is a succulent plant and available in many regions of India as well as throughout the world. The leaf parts of *aloe vera* produce latexes and shows good cathartic property. In case of their availability it is available in two forms one is pure and second is unpure form in the market; also the ingredients have been variety of formulations available in the market [4]. (Barbaloin is also called as aloin, Figure 2), there is upto constitute up to 30% of the dried leaf part and planned as a useful part for defense mechanisms for herbivores [5]. The leaf extract of barbaloin access to inhibit the growth of Mycobacterium in case tuberculosis, and this is happening because of the bio-active metabolites in barbaloin [6]. This phytoconstituent is not phototoxic, in human skin the fibroblasts are present and they can help to metabolize aloin to aloe emodin [7].



Figure 2: Location of aloin in *aloe vera* plant leaf.

The investigation shows that *aloe vera* gel contains low molecular weight and toxic compounds. In this review article all these efforts are made regarding the achievement and limit the amount of all these toxic compounds in *aloe vera* products [8]. In the starting decade we discuss about the content availability in young and older leaves of aloe species [1]. As we know it is the C-glucoside of aloe emodin anthrone that is available in the outer division of the *aloe vera* plant. The constituents are very much used against herbivores and the 30% constituents were presents in the leaf exudates of the plants. [2].The surety of the

major ness of this phytoconstituent is accessed by the HPLC analysis of the Aloe vera leaves and it is reported to contain Barbaloin as major constituents [9, 10]. The Examination of their surety index is based on the previous literature that showed us lack of methods to analyze the commercial products of Barbaloin. In HPLC analysis it is establish that barbaloin is the major bioactive compound in aloe species [11]. The use of *aloe vera* as ingredients of cosmetics and the concern over the barbaloin content as it shows phototoxic effect in such preparations and also its beneficiary effect in ayurvedic formulation.

Extraction Methods of Barbaloin

The extraction of *aloe vera* is done by collecting the fresh leaves from the local nursery after that the rinds are removed from leaves by washing with clean water. The obtained inner gel were scrapped and cut into small pieces. A long process of drying is processed by solar drying at 30-45°C for 3 weeks and in last the dry gel particles were collected or ready to screen. The screening of dry particles of gel is sieved under the various ranges of 0.42-0.841, 0.841 –1.68, 1.68-3.36 & 3.36–6.73 mm correspondingly. The Standard barbaloin were obtained with the help of Fluka method and Ultra assisted sonication method for the process of calibration. A variety of grades solvents are used in the analysis by HPLC, from S.D. Fine Chemcials, India. Ultrasonic probes which are made in Taiwan, 20 KHz and are having 1.5 cm diameter or 30.0 cm length were used in the process of sonication. Constant temperature will maintain under the vessel. Later than that, the samples were collected at a particular time of intervals to analyze the content of barbaloin in aloe vera [12].

Soxhlet extraction

The extraction of barbaloin was carried out in the methanol using Soxhlet extraction method. Mostly we take 0.42-0.841 mm dry gel particles (5% w/w) with 200 ml of methanol. Withdrawal of barbaloin was conceded in 24 hours. The dry Samples were collected inlast, stored in a freezer and analyzed with the help of HPLC to find out the concentration of barbaloin in every extract [13].

Batch extraction experiment

A 250 mL cylindrical vessel is used in the process of Batch extraction experiment. The vessel is made from borosilicate glass with the following dimensions eg: width-7 cm and height-9 cm. For the investigation of the extraction process it is

important to analyze persuades of the in use parameters of experiment. In next, the dry gel is filled into the vessel with 200 mL suitable solvent. A required volume of suitable solvent in every procedure was used in 200 ml quantity and the dry gel was loaded or altered consequently. For experimentation the 4 pitch bladed 450 turbine agitator with diameter of 3.5 cm and the mass will obtained with the help of diameter at different rpm. The experiment was performed in a thermostatic bath and the accurate temperature is maintained. The sample was collected in diverse time process till the final extraction process and the samples are analyzed with the help of HPLC and it will useful to find the accurate concentration of our phytoconstituent. In last of each procedure, collect the filtered substance to adjust the volume of vessel a makeup at its original value to remove the errors in the concentration of barbaloin by the loss of vaporization process. The impact of the solvent system by unreliable polarity (e.g. ethanol, water, and methanol and Iso-propyl alcohol) and the speed of process of agitation are relatively in the range of 300, 600, 900, and 1200 rpm. The particle size is in the range of 0.42-6.73 mm and the solid loading is in the range of 2.5 -10%. The temperature is in the range of 30°C-65°C). All these parameters are used for investigation and it will help us to select the best possible situation for the batch extraction process [13].

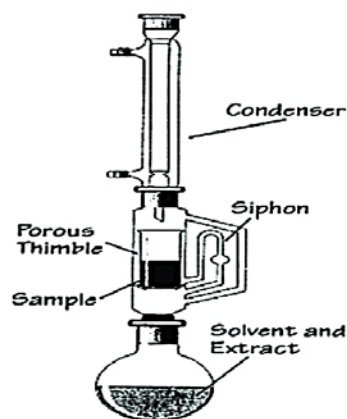


Figure 3 Soxhlet extraction apparatus [14].

Extraction method assisted with Ultrasound (UAE)

In the extraction of some bioactive compounds that are taken from herbs, plants sources etc [15, 16, 17, 18]. Ultrasonic extraction enhances the production of micro cavitation on liquid nearby the plant substance. All the effects are mechanically disreputable to the cell wall of substance that will release the content and produce local heating to liquid material; also the diffusion rate will increase. The kinetic energy during the

process and ultrasound isolation induces in the complete volume and subsequently disintegrates of cavitation in bubbles at solid or liquid interface can improve the transfer of mass across widely [19].

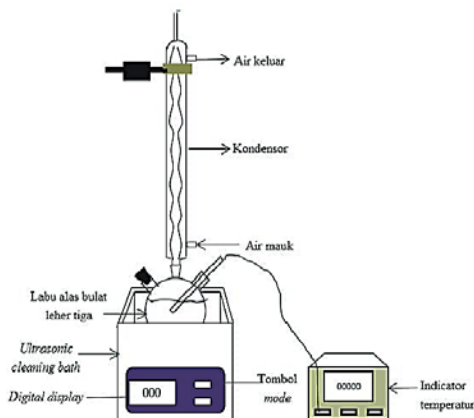


Figure 4: Ultrasonic assisted extraction apparatus [20]

In comparison with batch extraction experiment, the rate of extraction process much improved in this experiment. The time of extraction and temperature will decrease and in other side the extraction rate will increase. This experiment was performed to take the active phytoconstituent from plant. For Ultrasonic assisted extraction methanol is the selected as solvent which is a good organic solvent and it will use in the extraction process of barbaloin. The active principle aloin was quantified using WATER's HPLC system. For the better experimentation necessary conditions are required and they should be maintained as temperature, time of extraction as well as the loading of dry gel. The diffusivity of impassive internal particle of barbaloin in an organic solvent (methanol) was examined under diffusion model. So to find the activation energy of diffusion the Arrhenius equation was used [12].

Medicinal importance and Pharmacological activities of Barbaloin

Barbaloin is the main and active phytoconstituent of plan *Aloe Vera* and it is widely used in many proposes. Because of its good multitasking nature is can be used as a variety of major disease treatment. According to the study barbaloin shows good and effective medicinal and pharmacological properties. The following efforts are maintained to understand the power of barbaloin in many diseases, due to its antiinflammatory, antidiabetic, antioxidant, anticancer, antimicrobial activities it is helpful and effective constituent [19, 21]. The effective properties of barbaloin are listed in the Table 1.

Table 1: List of Various Pharmacological and Medicinal Properties of Barbaloin

Properties of Barbaloin	Mechanism of Action	Ref.
Anticancer Property	Inhibit the activation of Nuclear factor-kappa B p65 cells, and down regulate the expression of Nitric Oxide Synthase mRNA	[22, 23]
Antidiabetic Property	Necrosis on beta cells into the pancreas is induced with streptozotocin which show the anti-diabetic activity of barbaloin	[24, 25]
Antiinflammatory Property	Inhibit the (ROS) mediated (JAK1-STAT1/3) and activate the signaling pathway.	[26]
Antioxidant Property	Decrease in the influence of free radical effects of barbaloin and protect the component of DNA.	[27]
Antimicrobial Property	Barbaloin inactivates the enzymes of bacteria which showed their antimicrobial property.	[28, 29]
Impact on Cardiovascular	The potent hypotensive effect of Barbaloin is due to the arterial blood pressure fall.	[31]
Impact on Test Perception	The 25G polymerase chain reaction-Protein Coupled Receptors and results to change in the taste sensation of barbaloin.	[32]
Impact on Enzymes	Reversibly and noncompetitively inhibit then <i>Clostridium histolyticum</i> collagenase and stimulates the granulocyte matrix metalloproteinase's	[33, 34]
Impact on Metabolism and Bioavailability	Increase in the rates of elimination of blood alcohol throughout the body.	[37]

Anticancer Property

The examination of the effect of barbaloin on the capability of cells was obtained through Jurkat T cells. When we give a treatment of barbaloin to the cancer patient it will help us to reduce the size of cell, compromising the integrity of skin

membrane and also it may cause the potential loss of the membrane of mitochondria as an effective dose reliant manner. Moreover, the alteration of cell cycle is occurring during the process of cancer patient treatment with barbaloin. When the cell membrane integrity were started there is a loss of integrity in cell membrane by the potentially loss of mitochondrial membrane and this term suggesting us a mitochondrial-dependent pathway for barbaloin induced apoptosis. The defensive mechanism of barbaloin on Nitric Oxide Synthase is the factor that is known as nuclear factor- kappa B. It helps in the human keratinocyte cells syntheses that are induced by the examination of UV-B irradiation. When the Nuclear factor- kappa B p65 receptors are activated then the inhibition of proliferation effect of human keratinocyte cells in body is suddenly increased. Now it will sure that barbaloin successfully treat and inhibit the activation of Nuclear factor-kappa B p65 cells, and down regulate the expression of Nitric Oxide Synthase mRNA and nitric oxide production is induced due to irradiation of UV-B. Barbaloin was also investigated for the cytotoxicity studies based on low molecular weight fractions. The comparison of toxicities was done for the barbaloin and aloe-emodin with Sodium Dodecyl Sulfate by the use of chemiluminescence assay results showed that compounds showed some toxic effects [22]. The effective purified compounds including barbaloin from Aloe plant on variety of variants like human K562, leukaemia or in the multidrug resistant variant, the K562/R variant were studied by invitro process. In aloe species the compounds which are responsible for producing the antitumor activity name as aglycone and aloe emodin show reproducible antitumor effects. Both the compounds are fascinatingly were more approached in multidrug resistant and P-glycoprotein to overcome the expressing of cell line [23].

Antidiabetic Property

The extract of *aloe vera* contains high concentration of some polyphenols and with that the well-known ratio of Barbaloin is present. Barbaloin delivered by oral route still from long period of time upto 4weeks to the insulin resistance mice. The results confirms the polyphenols are the richest source that is extracted from *aloe vera* plant and it will surely effective to control or minimize the level of blood glucose or also decrease the weight of mice in comparison with mice in controlled group. In the study the mice which are treated with barbaloin showed the highest level of glucose as compared to the control group of mice treated with pioglitazone [8]. In another investigation the

defense mechanism of aloe species like barbaloin that is isolated from aloe plant. The necrosis on beta cells into the pancreatic islets of mice are induced with streptozotocin were examined and help us to clarify the anti-diabetic activity of barbaloin [24].

Antiinflammatory Property

In the present investigation the effect of the antiinflammatory property of barbaloin is compared. During research, the results showed that a dose-dependent effect of barbaloin slow down the nitric oxide synthase effect, expression of mRNA and the making of nitric oxide (NO). The nitric oxide production is also covered; also they do not reproduce the Prostaglandin-E2 manufacture. Our investigations suggest that Barbaloin the inflammatory activity of barbaloin were suppressing by blocking the mRNA expression of nitric oxide synthase effect and the effect of Cyclooxygenase-2 mRNA in body [25].

Antioxidant Property

Barbaloin behave like an antioxidant system on the site of free radical that may induced with deoxyribonucleic acid component. Barbaloin also protect the OH-induced components of deoxyribonucleic acid and breaks it to compared with the another control group. In the lower concentrations it increases the deoxyribonucleic acid damage or indicating its antioxidant property. The highest effect of barbaloin is reduced in minimum ratio. On the other side, there is gradually decrease in the power of free radical effects of barbaloin and that may lead to results to protect the component of deoxyribonucleic acid [26].

Antimicrobial Property

The phytoconstituent barbaloin showed good antimicrobial property and the extract is very effective against *N. gonorrhoea*. In other hands the pure barbaloin repressed the microbial growth [27]. In Aloe plant the toxic index of 34-Aloe species were found and the main phytoconstituent is barbaloin which showed very good anti-plasmodial effect. Barbaloin showed good activity in front of chloroquine resistant *Plasmodium falciparum* strain. The effective inhibitor to control the growth of parasites is more in homonataloin than barbaloin [28]. In another study barbaloin combined with *W. somnifera* showed antiviral activities against type 1 herpes simplex [29].

Impact on Cardiovascular System

In the aloe species the hypotensive activity of components like *aloin A*, *aloe emodin*, and other is bisbenzopyran all these

constituents are investigated from aloe plant. The constituent who showed good Hypotensive activity known as Aloe emodin and it has been recognized as a strong hypotensive component in available pharmacology [30].

Impact on Test Perception

According to the taste of human there is a famous observable fact for the bitter taste and it is supposed to be produced from the 25G polymerase chain reaction-Protein Coupled Receptors family. During Polymorphism between two hours the hydroxy tryptamine-2R genes results to show varieties of activities on different receptors. By change in the taste sensation of some bitter substances the taste of barbaloin is also changed. The hydroxy tryptamine-2R43 protein encodes in position 35 with tryptophan and it will make people very responsive for the bitter taste of barbaloin along with aristolochic acid [31].

Impact on Enzymes

In the present study the effect of barbaloin on enzyme and hyper pigmentation were explained. The effective uses of Tyrosinase were estimated by calculating the rate of oxidation of Levodopa. The reticence rate tyrosinase or barbaloin in different levels is greater than hydroquinone compound [32]. The phytoconstituent barbaloin reversibly and noncompetitively inhibit the Clostridium histolyticum collagenase. Barbaloin is the effective inhibitors because it stimulates the granulocyte matrix metalloproteinase's. According to their structural resemblances between both the compounds barbaloin and tetracyclines, they suggest that barbaloin shows inhibitory effect by via a relation between two groups, carbonyl on C9 position and anthrone on C1 or C8 binds with enzyme at their secondary site [33].

Impact on Metabolism and Bioavailability

The intestinal absorption model is used to find out the metabolic effect of barbaloin [34]. A rat model is used to find the bioavailability of barbaloin. The barbaloin level and their conjugative were estimated in the following pattern like plasma, tissues, and urine. In the current study we find that the time to absorbed barbaloin to reach the peak plasma level is about 1-1.5 h later than the administration and some portion is possibly metabolized and excreted through feces [35]. The effect of barbaloin into the blood and level of alcohol was identified with the help of female rats. If there is an increase in the rates of elimination of blood alcohol throughout the body were originate with the treatment of barbaloin. Pretreatments with the help of

can results in decrease the level of blood alcohol (Area under curve) and there is an increase in the rate of departure of ethanol [36]. To evaluate the digestive constancy or in the absorption of barbaloin with other aloe constituents, the in vitro model fitted with cancer coli-2cell was used in the current identification. Barbaloin and other constituents were elated with apical and basolateral compartments later than 1 hr of incubation into the cancer coli-2 cell [37].

Potential of Barbaloin on the treatment of skin disorders

Human skin is the major widespread, extensive and diverse organ of our body. Skin is helpful to defend the body from external harmful environment. Sometime our skin may be affected by much dermatitis and these factors may harm to the spiritual state of the peoples [37]. According to research both the factors was played a crucial role in development and effective treatment of many chronic skin disorders in Table 2.

Table 1: List of various kinds of skin disorders with their sign and symptoms

Skin Disorders	Sign and Symptoms
Eczema	Dry, Itching, Red to brownish-gray patches develop on hands, feet and eyelid.
Psoriasis	Slivery scales or red patches cause inflammation, pain and itching to the skin.
Burns & wound	Skin redness, peeling, blister are formed and pain in mild to moderate disease.
Acne	Closed and open plugged pores or pus filled papules are formed in the skin,
Dandruff	Small white, greasy or yellow flakes are developed around the hairlines of skin.
Frostbite	Pricking feeling, numbness and hard or waxy-looking skin, muscles stiffness.
Rashes	Itching, redness, dry, scaly skin and formation of small liquid filled blisters.
Cold sores	Tingling, itching and burning sensation around the lips and blisters formed.
Razor burn	Rashes, redness, itching, burn sensation and red bumps around the skin.
Sunburn	Pinkness or redness on skin and pain, headache, fever and nausea can occur.

Eczema

It is also called dermatitis, is a skin condition that causes patches of itchy, irritated skin. Here are many types of eczema. Some cases are a response to an allergen or irritant, while others don't have a clear cause. The barbaloin known to have both antibacterial and antifungal effects trusted source. This, combined with its anti-inflammatory properties, could be particularly useful for people with eczema. Irritated, broken skin is more prone to bacterial and fungal infections [38].

Psoriasis

Barbaloin gel is obtained from the *aloe vera* plant. This phytoconstituent Barbaloin found to have an effective antipsoriatic activity, soothing effect to skin. Barbaloin gel is also having an antibacterial effect on skin diseases. The effective nature of barbaloin has ability to treat psoriasis [39].

Burns and wound

Mohammad Reza Akhoondinasab et al., revealed in their study that if there is any burn and wound noted on skin then Barbaloin has been excellent property to heal them. The possible mechanism for the healing may be due to increasing blood flow, decreasing the rate of infections and decreased inflammatory response. [40].

Acne

Barbaloin is effective for the treatment of Acne due to their antibacterial properties. It's been used for centuries to treat acne. Very few people are allergic to it and applying it topically because of its minimum side effects [41].

Dandruff

This phytoconstituent is well known for its moisturizing effect on dry skin, and anti-inflammatory actions that may help to reduce irritation or inflammation when applied to the skin. The antioxidant property of barbaloin can prevent cell damage. So, this is effective for the treatment of mild to moderate dandruff [42].

Frostbite

The term frostbite is generally related to skin disorder and usually develops on some parts of our body eg: ears, nose, cheeks, fingers and chin. The symptoms of frostbite are developing when your skin is contact with freezing temperatures ($\leq 32^{\circ}\text{F}$). During this disorder generally the unending damage and death of tissue had been seen. Barbaloin is very much useful

in the treatment of frostbite due to their anti-inflammatory effects. Barbaloin can effectively support and may helpful in the process of tissue healing and also it can make new cells that are healthy by nature or good to treat frostbite symptoms in a more speedy and effective way [43].

Rashes

Rashes are commonly red in color and they cause inflammation to the skin. There is various causes of forming rashes eg; imbalance in immune system, some allergic reactions by harmful environment. Due to the anti-inflammatory and antimicrobial activity of barbaloin it is use in the treatment of rashes. The common irritation on the skin develop rash and the barbaloin is effective to soothe inflammation of rashes. This will improve the appearance of the rash, too [44].

Cold Sores

In the intervening time, cold sores are commonly developed due to virus. They are usually decreased in some days but also affected many people's they are generally developed nearby the lips and vary in different sizes. They are infectious to the touch. Due to the great anti-inflammatory property of plant *aloe vera*, it can generally increase the healing property or decrease the pain which is related with canker sores [45].

Razor Burns

Aloin is known for its anti-inflammatory activity and it also has good soothing property. To treat razor burn, the *aloe vera* gel can apply on infected skin it can help to reduce the symptoms [46].

Sunburn

A compound in aloe called barbaloin was found to be responsible for the plant's anti-inflammatory benefits. Barbaloin can also help to moisturize the skin and prevent the peeling that sometimes happens with sunburns. It very much effective for the healing of burns, mainly mild to moderate types of sunburns [47].

DISCUSSION AND CONCLUSION

The herbal phytoconstituent are normally obtained from plant sources and they are responsible for color variation and plant odour. They are naturally protect and played a key role in the defensive mechanism related with many diseases. Barbaloin is the phytoconstituent which is present in the plant *aloe vera* and found easily throughout the world. It plays a significant role in

medicine and health care system because it is best known for its medicinal properties. In this study barbaloin is isolated from *aloe vera* by Soxhlet extraction, batch extraction experiment and Ultrasound assisted extraction method. A suitable solvent system is used to isolate the compound. Barbaloin mostly dependable for its pharmacological behavior and plays an effective toward defensive mechanism on diseases. The various phytoconstituents have been technically evaluated for their antioxidants, anti-inflammatory, anticancer, antimicrobial and antidiabetic activities. Study also showed that Encouraging effect of barbaloin was evaluated on metabolic system, cardiovascular systems and other enzymes systems. Due to the effective medicinal value and good pharmacological activity the barbaloin have great potential to treat various skin disorders like Eczema, Psoriasis, Burns and wound, Acne, Dandruff, Frostbite, Rashes, Cold sores, Razor burn, Sunburn etc. From the available literature data, it was concluded that barbaloin have valuable pharmacological activities and could impactfully admitted for the treatment of various skin disorders. In our present review, data were collected for barbaloin in reference to their medicinal importance or pharmacological activities and its extraction procedure or potential to treat skin disorders. This data could be helpful for understanding traditional and modern application of barbaloin.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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