

APPENDIX 1

FLAVONOID DERIVATIVES USED TO TREAT ECZEMA

Project Report submitted in partial fulfillment

for the award of the degree of

BACHELORS OF PHARMACY

Submitted by

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(Established under Galgotias University Uttar Pradesh Act No. 14 of 2011)

APRIL/MAY 2020-21

APPENDIX 2



SCHOOL OF MEDICAL AND ALLIED SCIENCES

BONAFIDE CERTIFICATE

Certified that this project report **“FLAVONOID DERIVATIVES USED TO TREAT ECZEMA”** is the bonafide work of **“ANINDITA CHAKI (1712102012)”** who carried out the project work under my supervision.

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SUPERVISOR**

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Approval Sheet

This thesis/dissertation/report entitled ‘flavonoid derivatives used to treat eczema’ by Anindita Chaki is approved for the degree of Bachelors in Pharmacy

Examiners

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Date: _____

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Statement of Project Report Preparation

Thesis title: Flavonoid Derivatives used to Treat Eczema

1. Degree for which the report is submitted: Bachelors in Pharmacy
2. Project Supervisor was referred to for preparing the report.
3. Specifications regarding thesis format have been closely followed.
4. The contents of the thesis have been organized based on the guidelines.
5. The report has been prepared without resorting to plagiarism.
6. All sources used have been cited appropriately.
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ABSTRACT-

Eczema is a systemic autoimmune disease, characterized by inflammation and skin manifestation with a range of comorbidities that include other physical and psychological disorders. Despite recent advancements in understanding the mechanisms involved in Atopic Dermatitis, current marketed products show varying results with more side effects.

The present objective of the research studies is to develop new eczema agents that cuts down the cost of the novel drugs available and also improve the efficacy with least adverse effects.

Natural compounds and medicinal plants have been traditionally used since ancient civilization. Earlier used most commonly in rural areas, nowadays researches in the herbal field is on its peak. One such natural compound, flavonoids are found to be beneficial for the treatment of eczema.

The article describes the use of certain flavonoid products to prepare preparations suitable for the treatment / treatment of prophylaxis or eczema. This is especially true for prophylaxis or atopic eczema treatment. These compounds exhibit anti-inflammatory, anti-inflammatory, anti-inflammatory and anti-inflammatory properties and are therefore used in treatments or treatments to prevent allergies, inflammation and irritation to the skin. We have also docked the flavonoid derivatives used with the protein associated with the inhibition of eczema for better lead optimization.

These preparations appear to be used for cosmetic, dermatological or herbal remedies used as a local application.

Hence this review summarizes the published literature on five common flavonoid derivatives; Kaempferol, Tiliroside, Hesperidin, Curcumin, Apigenin used for the treatment of eczema. The review deals with the source, antioxidant activity and the therapeutic action of the flavonoids. A brief information about the molecular docking results has also been provided with the protein associated with the inhibition of eczema.

Keywords - Medicinal Plants, Flavonoids, Eczema, Dermatology, Treatment, Dermatitis, Prophylaxis, Herbal

GRAPHICAL ABSTRACT-

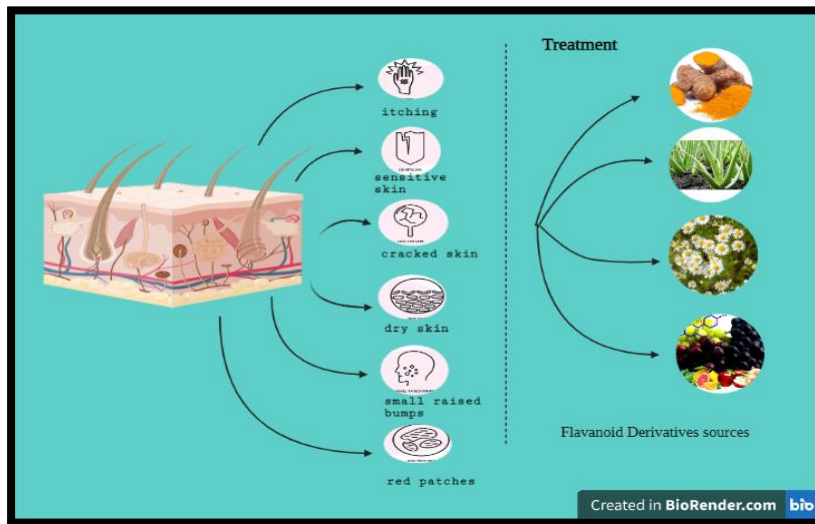


Fig 1: Graphical Abstract

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CHAPTER 1

1.INTRODUCTION

Spread in perfect place for approx. 20 square feet, the largest organ of the body, the skin that protects living organisms from microbes and other elements. The organ aids in healing, and allows sensations of touch, heat and cold. [8]

The skin has three layers:

- The epidermis is a layer of outer skin that provides a waterproof barrier and creates a skin tone.
- Skin, lying under the skin containing hard connective tissue, hair follicles and sweat glands.
- Hypodermis, which contains subcutaneous tissue made of fat and connective tissue.[1]

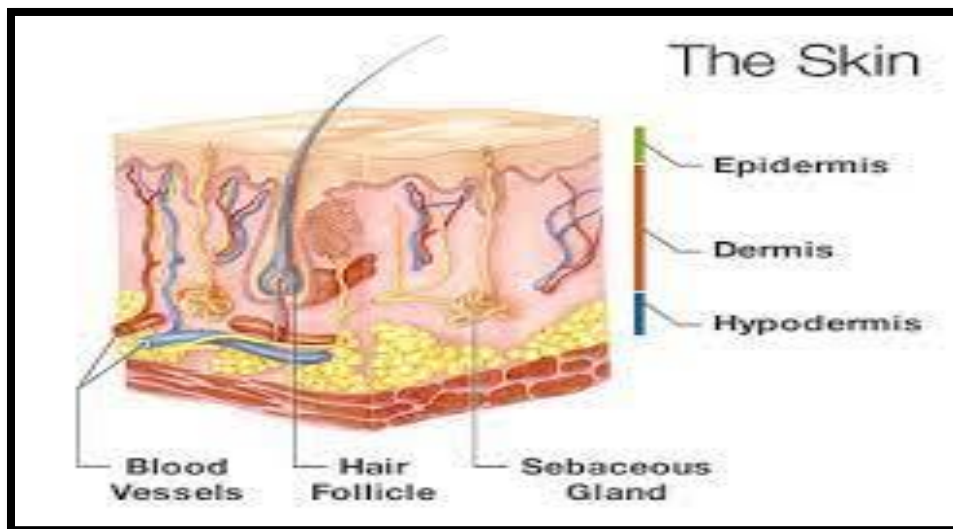


Fig 2: Skin

In the midst of skin irritation, we see areas of skin that are swollen, itchy, cracked, and aggressive. a skin disorder is called Eczema where we can see blisters. It is often seen as a result of an overactive immune system.

Numerous kinds of flavonoids are utilized to treat skin inflammation; be that as it may, we have chosen from this survey, the five most famous flavonoids, which can be utilized for the treatment/treatment of dermatitis. ^[1]

1.1 TYPES OF ECZEMA-

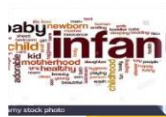
a) Atopic dermatitis.

The most widely recognized indications of atopic dermatitis are

- The rash normally shows up on the sides of your elbows or knees
- The skin turns out to be thick or dim in regions where there is a rash.
- The fluid can spill into little knocks, scratches
- Pimples on the infant's head and cheeks show up.
- the skin gets contaminated when irritated^[3]

The disease is most common in children, where dry patches of scalp appear in the form of skin infections. Eczema appears mild in most cases yet, a portion of the manifestations of dermatitis are diverse for individuals with brown complexion. Patients suffering from severe symptoms of eczema need extra cooling care to be treated. Children and adults in particular show different symptoms. ^[1]

The matrix mentioned below shows some of these differences in a clearer way-



Infants

- ❑ rashes appear on scalp and cheeks
- ❑ rashes get bubbled up before the fluid leaks
- ❑ rashes cause intense itchiness
- ❑ this might interfere with sleep



Children

- ❑ rashes
 - ❑ that show up behind the wrinkles of elbows or knees
 - ❑ rashes that show up on the neck, wrists, lower legs, and the wrinkle between the backside and legs
- ❑ rough rashes
- ❑ rashes that can get lighter or more obscure

- ❑ skin thickening, likewise known as lichenification, which would then be able to form into a perpetual tingle



Adults

- ❑ rashes that are more textured than those happening in youngsters
- ❑ rashes that usually show up in the wrinkles of the elbows or knees or the scruff of the neck
- ❑ rashes that cover a significant part of the body
- ❑ extremely dry skin on the influenced territories
- ❑ rashes that are forever irritated

- ❑ skin disease

Table 1: Comparative Symptoms of eczema

Causes: The most common causes of atopic dermatitis are:

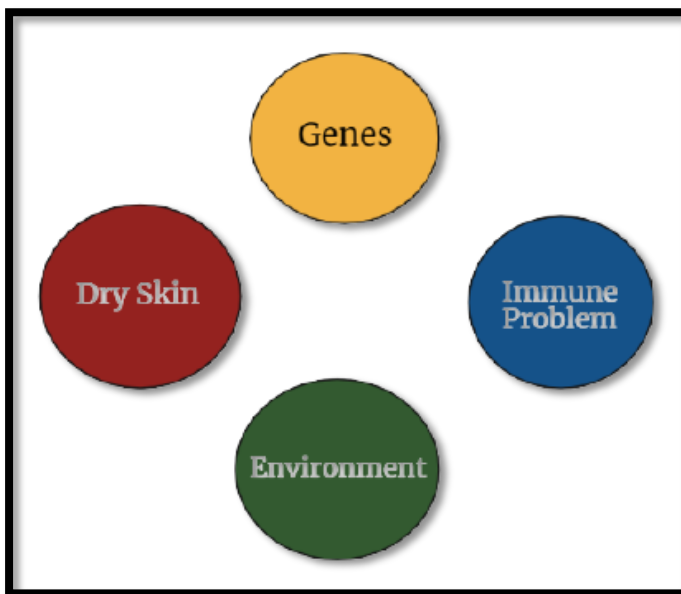


Fig 3: causes-Atopic Dermatitis

b) **Contact dermatitis** - skin, disappointed brought about by a response to the items you contact, might be indications of contact with dermatitis.

The most widely recognized manifestations of contact dermatitis are-

- bothersome skin, redness, sensation of warmth, and diminishing

- Biting bumps otherwise called chest agonies can show up on your skin
- Fluid-topped air pockets can work off and detonate
- Over time, the skin may thicken and feel skin or skin[5]

Causes- Point by point dermatitis happens when you contact something that aggravates your skin or causes an overactive response. The most widely recognized causes are:

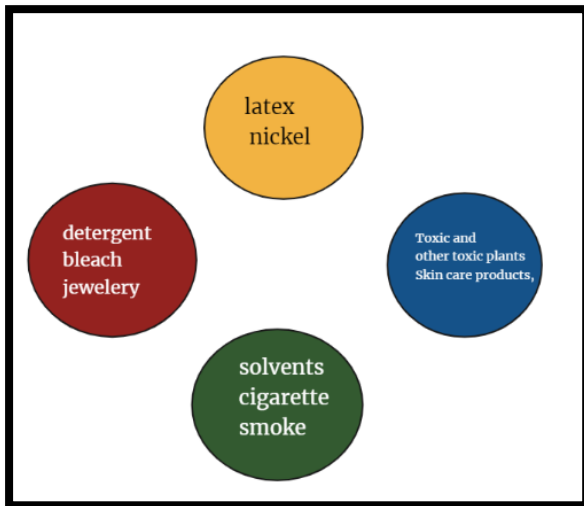


Fig 4: Causes- Contact Dermatitis

c) **Dyshidrotic eczema** - More normal in ladies than men, dyshidrotic dermatitis causes little rankles on all fours.

The most well-known side effects of dyshidrotic dermatitis are:

- Fluid-filled rankles on the fingers, toes, palms, and bottoms of the feet
- The rankles may chomp or be destructive
- The skin can gauge, break, break [3]

Causes-Dyshidrotic dermatitis can be brought about by:

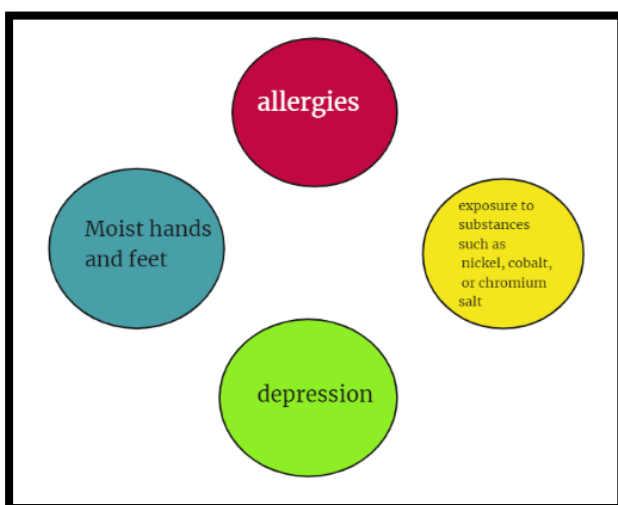


Fig 5: Causes-Dyshidrotic eczema

d) **Hand Eczema**-Dermatitis that lone influences the hands is called hand skin inflammation.

Side effects Hand skin inflammation:

- Hands are red, irritated, and dry
- structures breaks or rankles

Causes-Causes openness to synthetic compounds. Individuals who work in positions that open them to irritating things are bound to get this structure, for example,:

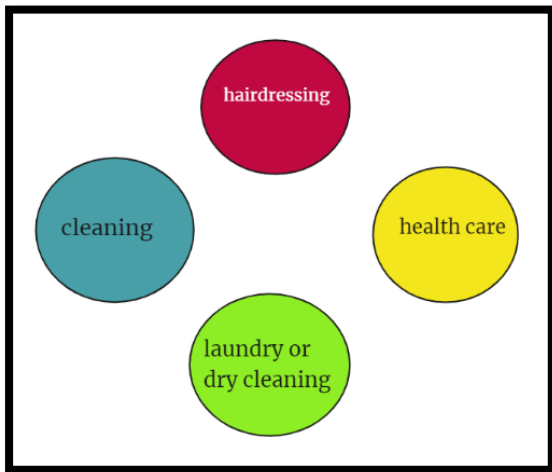


Fig 6: Causes- Hand Eczema

e) **Neurodermatitis**- like atopic dermatitis, causes thick, flaky spots on your skin.

Indications In neurodermatitis: thick structures, with scarves on the arms, legs, back of the neck, skin, feet, backs, or privates

- These patches can be exceptionally bothersome, particularly when the individual is loose or snoring
- If they are damaged, they can drain and get tainted

Causes-Neurodermatitis typically starts in individuals with different types of dermatitis or psoriasis.

f) **Nummular eczema** - This sort of dermatitis causes round, monetary spots to frame on the skin. Nummular skin inflammation appears to be exceptionally unique from different kinds of dermatitis, and is normally nibbled.

Side effects In nummular dermatitis:

- Round, coin-molded structures on the skin
- spots might be bothersome or difficult

Causes-

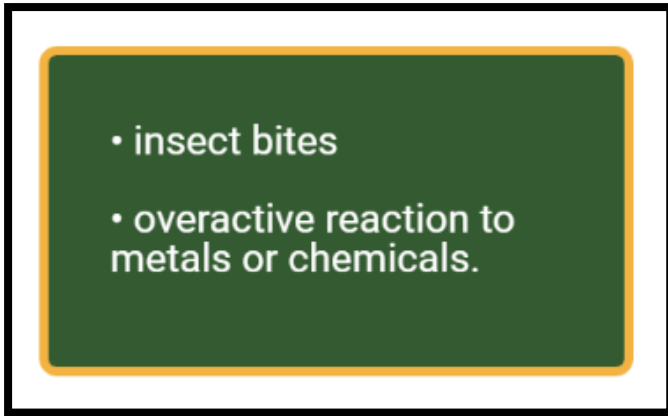


Fig 7: Causes- Nummular eczema

g) **Stasis Dermatitis**-It happens when liquid breaks from the powerless veins into your skin. This liquid causes expanding, redness, tingling and torment.

Manifestations in Stasis Dermatitis:

- The lower some portion of the legs may get swollen, particularly during the day when an individual is strolling
- The feet may throb or feel weighty
- an individual may likewise have varicose veins, tight veins, harmed ropes in the legs
- The skin over those varicose veins will dry out and tingle
- May create open injuries on the lower legs and lower legs

Causes-

It happens in individuals with issues with blood stream to their lower legs. On the off chance that the valves regularly push blood up through your legs to your heart work, blood can get into your legs. Your legs can become swollen and varicose veins can shape.

1.2 SECTIONS OF ECZEMA

Eczema can be separated into three classifications:^[4]



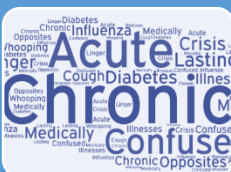
Chronic

- This is the most well-known phase of dermatitis, and it frequently creates in youngsters before they're 12 months old.
- Ongoing skin inflammation by and large endures over a long period with infrequent flare-ups, despite the fact that youth dermatitis may improve with age.



Acute

- Transient dermatitis might be the aftereffect of skin sensitivities subsequent to coming into contact with a bothering substance.
- Intense cases last only a couple a long time as your skin mends



Subacute

- This is essential for the recuperating period of dermatitis, which can in any case erupt back up into a full impulsive whenever left untreated.

Table 2: Sections of Eczema

1.3 PROBLEMS

•Asthma and roughage fever-Eczema at times goes before these conditions. The greater part of small kids with atopic dermatitis create asthma and roughage fever by age 13.

•Chronic itchy, scaly skin- A skin condition called neurodermatitis begins with a fix of bothersome skin. This condition can make the influenced skin become stained, thick and rough.

Irritant hand dermatitis

Skin infections- Continued scratching that tears the skin can cause open bruises and breaks.

•Allergic contact dermatitis- This condition is basic in individuals with atopic dermatitis.

Sleep problems^[2]

Table 3: Complications of Eczema

1.4 PATHOPHYSIOLOGY OF ATOPIC DERMATITIS

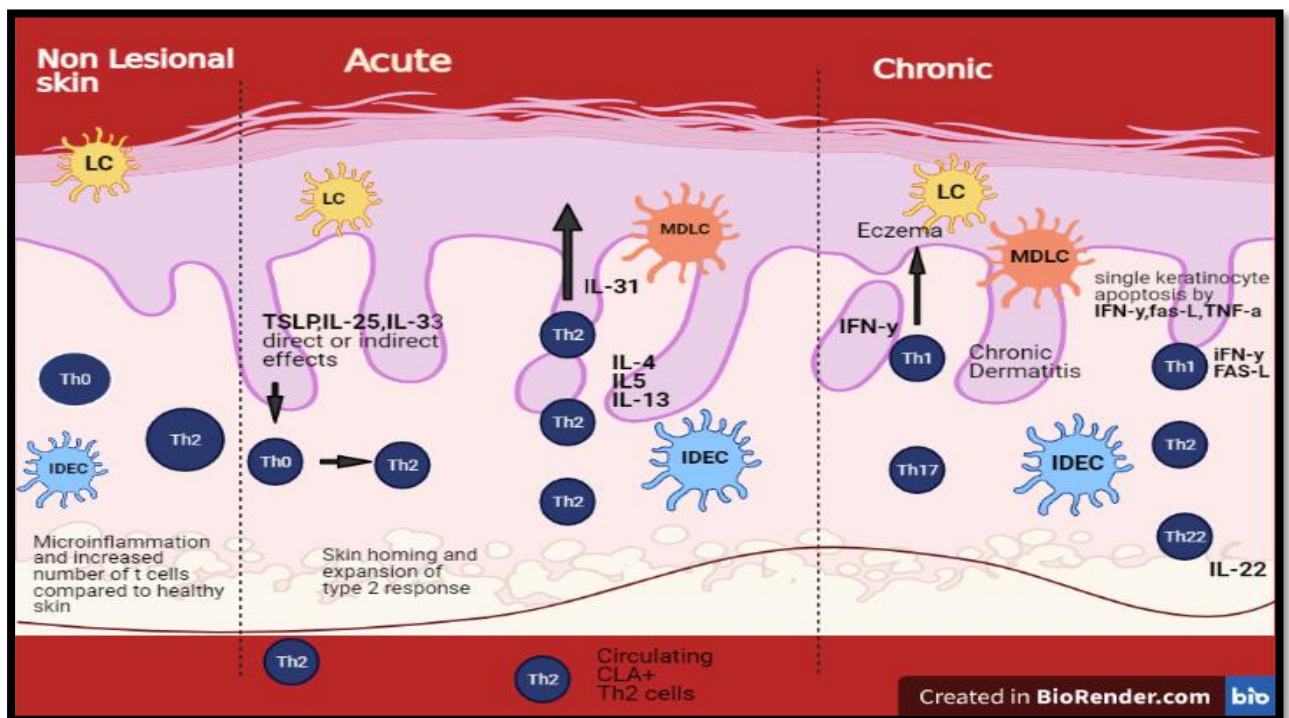


Fig 8: Pathophysiology of Eczema

Skin dryness and pruritus are 2 normal reasons for atopic dermatitis. It for the most part happens in individuals who are hereditarily influenced. Hereditary examination has

recognized the job of epidermal separation in atopic dermatitis. Changes in the hereditary construction of filaggrin, which are identified with a significant protein in the design of the epidermis, have likewise been noticed. The quantity of endogenic proteolytic compounds on the skin expansions in individuals experiencing atopic dermatitis. The skin surface diminished the measure of ceramides in both the influenced and unaffected zones. Ceramides are the primary water-holding cells inside the space of the earthenware cells. Skin conditions cause skin dryness that permits germs, antigens, and microbes to enter the body through little pores that lead to aggravation and disease. Moreover, immunodeficiency happens fundamentally in the 2 primary gatherings of CD4 + cells, T-assistant 1 and T-partner. The measure of eosinophils in the blood increments with an allergen or unfamiliar sort representing 70% to 80% of cases, patients have significant degrees of serum Ige. In 20% to 30% of patients, there is no critical expansion in Ige level, and accordingly, it is called nonallergic or interior sort of atopic dermatitis. Inward sort can be an indicator of outer atopic dermatitis. In this condition, the invulnerable framework prompts issues identified with the skin's insusceptible framework. These issues thus lead to more issues that wind up being replied in a strange manner by irritating things, admonitions, and natural things.[6]

1.5. FLAVANOIDS-

Flavonoids are a gathering of plant metabolites that give medical advantages through cell distinguishing proof instruments and cancer prevention agent impacts. Found in an assortment of foods grown from the ground, flavonoids are polyphenolic particles that contain 15 carbon iotas and break down in water. They comprise of two benzene rings associated by a short chain multiple times short. One of the cupboards in this arrangement is associated with carbon in one of the benzine rings, either by an oxygen connect or straightforwardly, which gives a third focal ring. Polyphenolic atoms can be separated into six significant subtypes, including chalcones, flavones, isoflavonoids, flavanones, anthoxanthins and anthocyanins. A considerable lot of these atoms, particularly the antanthropy, turn the yellow shade of specific leaves, while the anthocyanins frequently produce the rosy purple shade of the leaves and the red of the fall leaves. Flavonoids are plentiful in plants, where they play out a few capacities. The piglets are significant in creating the tones expected to pull in pollinators. Explains the use of certain flavonoid ingredients in preparations for prophylaxis and / or eczema treatment, most suitable for prophylaxis and / or atopic eczema treatment. [5]

1.6 S.A.R OF FLAVONOIDS –

General structure of flavonoids that normally contain hetrocyclic ring which is Benzopyran (oxane containing ring) in which benzene is intertwined with pyran.

At second position we notice the phenyl ring that will appended with the side chain now this is the overall construction of the flavonoids which can be altered at the diverse for instance one of the significant adjustment is the adjustment of the area of phenyl ring now here we can see that that the phenyl ring connected to the fundamental chain t the second position however this phenyl ring can likewise be available at the 3r position where they are additionally called as flavonoids yet they are isomers of these flavonoids so we need to utilize the prefix 'iso' so they are usually known as isoflavonoids.

Additionally other adjustment are immersion of twofold connection Between the second and third carbon a presentation of ketone or OH bunch at fourth position and replacement of the OH bunch at the diverse situation on the phenyl rings by these change we can notice such countless sorts of flavonoids which are available in the different kinds of plants

Flavone: It contain Ketone group at 4th position that's why they are having suffix one and the basic ring system is flavonoids so the prefix flav so it commonly called Flavone.

Flav + one → Flavone

There are 4 different types of flavone such as:

- Chrysin = 5,7- dihydroxy

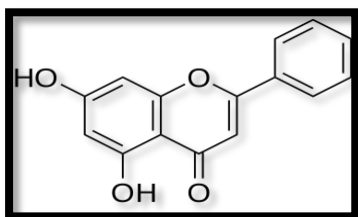


Fig 9: Chrysin

- Apigenin = 5,7,4'- trihydroxy

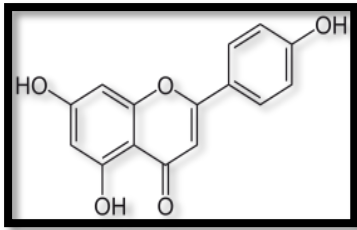


Fig 10: Apigenin

- Leuteolin = 5,7,3',4'- tetrahydroxy

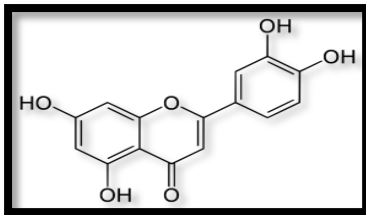


Fig 11:Leuteolin

- Tricetin = 5,7,3',4',5'- pentahydroxy

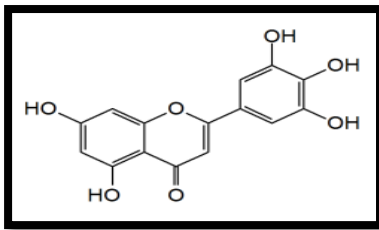


Fig 12:Tricetin

2. Flavonol: It contain hydroxyl group at the 3rd position now they are having both ketone at the 4th position and OH group at the 3rd position . So that's why we can compile the name as Flavonol.

Flav + one + ol → Flavonol.

Different types of flavonol are:

- Kaempferol = 3,5,7,4'-tetrahydroxy

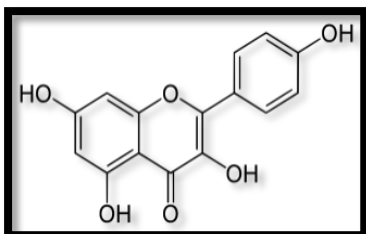


Fig 13:Kaempferol

- Quercetin = 3,5,7,3',4'-pentahydroxy

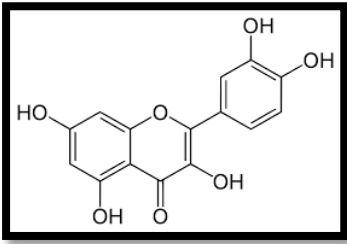


Fig 14:Quercetin

3. Isoflavone:- It contain phenyl group at 3rd position while in all other flavonoids phenyl ring is present at the 2nd position.

Iso + flav+ one →Isoflavone

Types of isoflavone are –

- Daidzein= 7,4'-dihydroxy

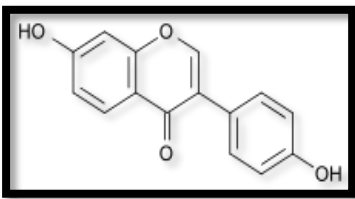


Fig 15:Daidzein

- Genistein= 5,7,4'-trihydroxy

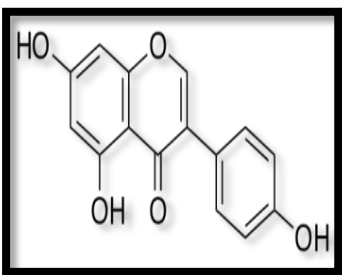


Fig 16:Genistein

4. Flavanone:- At 2nd and 3rd position there is a saturation that's why the name is some what modified now the name is;

Flav+ane +one →Flavanone.

Types of Flavanones –

- Naringenin = 5,7,4'-trihydroxy

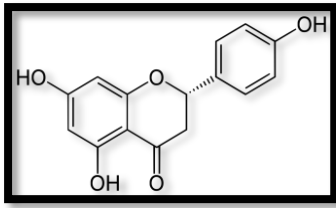


Fig 17: Naringenin

- Hesperitin= 5,7,3'-trihydroxy-4'-methoxy

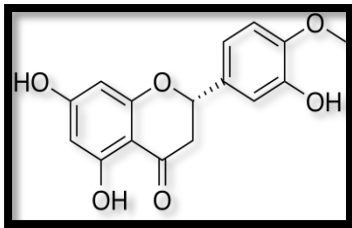


Fig 18:Hesperitin

5. Flavan-3-OL:- Here we observe saturation between 2nd and 3rd carbon and extra OH group at the 3rd position so now the name is Flav+ane+3-OL→Flavan-3-OL

- Quercetin= 3,5,7,3',4'-pentahydroxy flavan

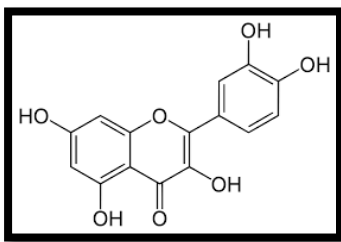


Fig 19:Quercetin

6. Anthocyanidins:- OH group at the 3rd position and an extra double bond says that they are forming a oxonium ion now they are made up of Flavyl ring system and the positive charge on the oxygen can be represented with the suffix ium. So this ring is nothing but the Flavyl+ium→Flavylum.

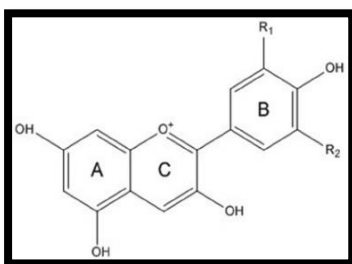


Fig 20:Anthocyanidins

Anthocyanidins are flavylum ring framework where auxim is getting the positive charge. So this is one of the construction cyanidin. cyanidin is very much like the quercetin its precise OH bunch at the 3,5th and seventh situation just as another OH bunch at third position and fourth situation on the phenyl ring however it is a cation with a positive charge on th oxime so cyanidin is 3,5,7,3',4'- pentahydroxy flavylum.

CHAPTER 2

LITERATURE REVIEW

(Shadi T. Zaril et al,2015) Many medicinal plants are commonly used to treat skin diseases such as eczema, psoriasis, vitiligo, cellulitis, herpes and cancer. Herbal medicine is as old as civilization. Application of traditional herbal medicine is widespread in different regions of the world. It is more common in villages and desert areas where medical services are less accessible. Herbal treatments are generally perceived as effective and have few side effects. Research on herbal drugs in terms of controlled clinical trials in humans is still limited. Herbal clinical research optimistically opens new therapeutic avenues. Eczema is considered as a group of medical conditions that cause the skin to become inflamed or irritated. The treatment of eczema is complicated. Moreover, screening is essential to reduce any potentially harmful side effects on human skin and health. This review summarizes the published literature on four common medicinal plants, namely, aloe (*Aloe vera*), oat (*Avena sativa*), turmeric (*Curcuma longa*) and chamomile (*Matricaria chamomilla*) used for the treatment of eczema. The mechanism of action, therapeutic indications and side effects of these plants are described.[14]

AE is a major global public health problem, affecting 1%-20% of people worldwide. The prevalence of AE in adults is about 1%-3%, and 10%-20%, in children.^{[101][102][103]} AE is a worldwide public health concern with significant financial burden. AE is a chronic skin inflammation and its symptoms wax and wane with various manifestations. Individualized therapy for the patient should be implemented according to patients' age, severity and extent of AE, and distribution of the lesion. To control AE, in addition to main pharmacologic therapy, other measures such as cutaneous hydration, identification and elimination of aggravating factors, relief of pruritus, and patient education should be considered[104]

- **Cutaneous hydration**

AE is characterized by an impaired skin barrier with xerosis, which needs to be strictly controlled by cutaneous hydration. *FLG* gene mutations are commonly shown in AE patients, which decrease the natural moisturizing factors. Furthermore, the correlation between *FLG* gene mutations and AE severity is well known.^[105] Cutaneous hydration can help the skin retain water, improve barrier function, and relieve itch sensations.

- **Topical glucocorticoids**

Topical glucocorticoids are a mainstay therapeutic agent for AE. They are known to be one of the most effective pharmaceuticals in controlling AE symptoms, such as itchiness and inflammation

- Topical immunomodulators, tacrolimus and pimecrolimus, are nonsteroidal, topical calcineurin inhibitors.^[106] They bind to FK-binding protein and inhibit the production of cytokines from activated T cells and inflammatory cells. Tacrolimus and pimecrolimus appear to have an anti-inflammatory potential similar or slightly less than that of midpotency corticosteroids.[107]

- Cyclosporin is an immunomodulator which primarily acts on T cells. It binds intracellular cyclophilin and inhibits cytokine transcription.

- Methotrexate, azathioprine, and mycophenolate mofetil are recommended as systemic agents for the treatment of refractory AE. Methotrexate is a folate

antagonist, which inhibits inflammatory cytokine synthesis and cell chemotaxis and acts as an antimetabolite[108]

- IFN- γ acts to reduce IgE levels and downregulates Th2 cells. There have been reports that treatment with IFN- γ can lead to clinical improvements.[109][110]

- **Anti-CD20 therapy**

Rituximab is an antibody against CD20 which depletes B cells. Treatment with Rituximab improved skin symptoms in patients with severe AE, suggesting its potential role for B-cells in the pathogenesis of AE.^[111]

- **Anti-IgE**

Omalizumab is a monoclonal antibody which binds and neutralizes IgE. Some AE patients have shown clinical improvement with anti-IgE therapy, but others have experienced no response or even aggravation of their symptoms.^{[112][113]}

2.1 Antioxidant Activity of Flavonoids –

Antioxidants are compounds that protect cells against the damaging effects of Reactive Oxygen Species(ROS), such as singlet oxygen, superoxide, peroxy radicals and peroxy nitrite. –The antioxidative activity of flavonoids is connected with the structure of the molecule: the presence of conjugated double bonds and the occurrence of functional groups in the rings. –An imbalance between antioxidants and ROS results in oxidative stress, leading to cellular damage. –Flavonoids reduce the production of and quench reactive oxygen species (ROS) through: -Suppression of singlet oxygen; -Inhibition of enzymes that generate ROS (cyclooxygenase, lipoxygenase, monooxygenase, xanthine oxidase); -Chelating ions of transition metals, which may catalyze ROS production; -Quenching cascades of free-radical reactions in lipid peroxidation; -“Re-cycling” of other antioxidants. Due to their low redox potential, they can reduce strong free radicals such as superoxides, alkyl radicals, hydroxyl radicals^[56]

Oxidative stress has been linked to cancer, aging, atherosclerosis, ischemic injury, inflammation and neurodegenerative diseases(Parkinson’s and Alzheimer’s). –Flavonoids may help provide protection against these diseases by contributing along with antioxidant vitamins and enzymes, to the total antioxidant defense system of the human body.

–Antioxidant flavonoids- -Quercetin (a flavonol in vegetables, fruit skins, onions) - Xanthohumol(a prenylated chalcone in hops and beer) -Isoxanthohumol (a prenylated flavanone in hops and beer) –Among all the flavonoids, Quercetin is the most abundant dietary flavonol, and is potent antioxidant because it has all the right structural features for free radical scavenging activity.^[57]

2.2 FLAVANOID DERIVATIVES-

The development is related to the use of other flavonoid extracts in the preparation of prophylaxis and / or eczema treatments and preparations, which contain flavonoid derivatives. Atopic eczema is an eczema-related eczema, "constitutionally" hypersensitivity (Atopy), in which a specific eczematogen is not found. Skin manifestations of "atopic diathesis" are about the location and type of age-dependent response: in children such as Facial eczema, in school children and in adults such as neurodermatitis, in adults and scattered herds of papules (prurigo) in the trunk and limbs; and more subtle forms, e.g. Dermatitis sicca; Inflammatory skin changes are most effective with weak or moderate Glucocorticoid correction treated to counteract the development of chronic skin changes. However, stopping the glucocorticoid may allow an outbreak of the inflammatory response. A person may continue to apply ointments or creams that contain glucocorticoid, for a short time because the skin may shrink for more than a few weeks. The acne appeals to the need for other agents or supplements, prophylaxis and / or treatment for eczema, especially atopic eczema. In PCT / EP 02/01200 chemical exposure appears to be applied to a UV filter, and is used as an active ingredient to protect against oxidative stress and to prevent skin aging. Synthetic compounds show hypersensitivities, aggravation, irritation and against aggravation properties and can along these lines be utilized as a treatment or treatment to forestall sensitivities, irritation and bothering of the skin. Corrections appear to be used in cosmetic procedures, skin treatments, or pharmaceuticals. Common preparations contain a traditional leather contract and are tested according to the carrier for the intended use and possibly other active ingredients and ingredients. [8]The current app also provides for the use of topics-

- a) at least one formula item I,
- b) a leather carrier
- c) intentionally at least one dynamic fixings with healthy skin and/or calming impacts.

Preferred preparations include making at least one anti-inflammatory ingredient c), which is a better choice for glucocorticoids or tacrolimus. It has been shown that formula I plans and arrangements by their foundation are helpful in the treatment of atopic skin inflammation, for example, support cap, neurodermatitis, prurigo and dermatitis particularly have sicca included.

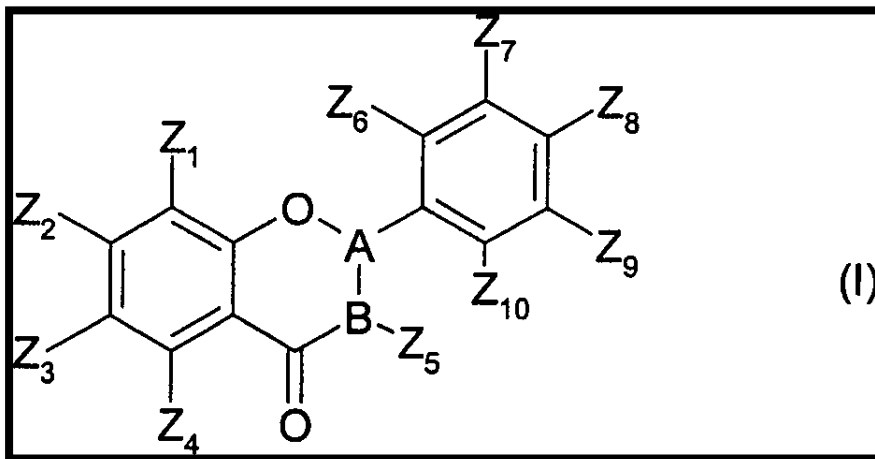


Fig 21: Formula I

Notable mixtures of the recipe I am, e.g., Kaempferol 3-(6 " - galloyl glucoside) and Kaempferol 3-(6 " - p-coumarylglucoside), otherwise called tiliroside.

Kaempferol-

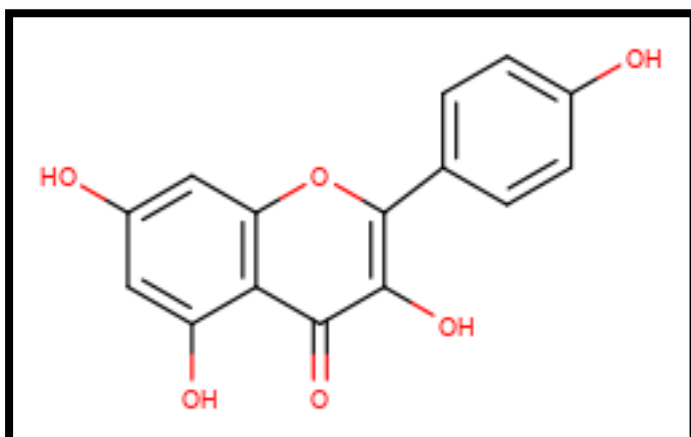


Fig 22: KAEMPFEROL

Molecular Formula-C₁₅H₁₀O₆

Weight-286.24 g / mol

Kaempferol is a flavonoid that is broadly dispersed in eatable plants and has been demonstrated to be genotoxic in V79 cells without outer stomach related frameworks. Kaempferol contains human metabolites known to incorporate (2S, 3S, 4S, 5R) - 6-[3,5-Dihydroxy-2-(4-hydroxyphenyl) - 4-oxochromen-7-yl] oxy-3, 4,5-trihydroxyoxane-2-carboxylic corrosive and Kaempferol-3-glucuronide. [9]

Kaempferol is a notable human metabolite of galangin and kaempferide.

Regular food sources containing kaempferol include: apples, grapes, tomatoes, green tea, potatoes, onions, broccoli, Brussels sprouts, squash, cucumbers, lettuce, green beans, peaches,berries and spinach.[10]



Fig 23: KAEMPFEROL-sources

Tiliroside-

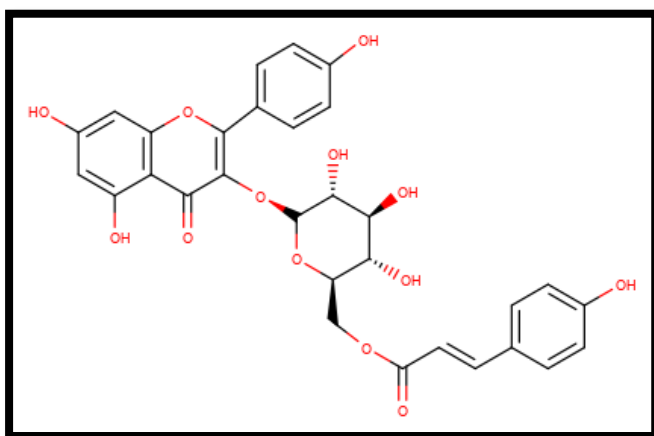


Fig 24: TILIROSIDE

Molecular Formula- C₃₀H₂₆O₁₃

Weight-594.5g / mol

Tribuloside is a glycosyloxyflavone kaempferol attached to 6-O - [(2E) -3- (4-hydroxyphenyl) prop-2-enoyl] -beta-D-glucopyranosyl residue in area 3 by glycosidic

bonding. It plays a role as a plant metabolite. It is glycosyloxyflavone, cinnamate ester, trihydroxy flavone and derived monosaccharide. It is found in kaempferol and trans-4-coumaric acid. Tiliroside acts as the first flavonoid to prepare tiliroside esters containing an acid unit containing 3 to 30 carbon atoms. These esters are utilized in makeup.[9] Furthermore, mixtures of the IA recipe, for instance, tiliroside, have a gentle to direct tone. The weak natural color, for example, is very useful if the natural color of the ingredients is not required in the products due to the aesthetic properties of tiliroside, can be separated from plants, for instance in plants of the class Althaea, Aristolochic, Helianthemum, Lindera Magnolia, Platanus, Potentilla, Quentilla, Quercida, Quercida/or Tilia. These mixtures can be prepared constantly or separately or segregation.[10]



Fig 25: TILIROSIDE-Sources

Structure Activity Relationship (Sar) of Tiliroside-

The biosynthesis pathways of TLD shows that the glycosylation stage changes the phenylpropanoid dissolvability, steadiness and harmful potential, just as impacting compartmentalization and natural movement [51]. Truth be told, glycosylation may forestall the poisonousness of aglycone phenylpropanoids as well as add to the creation of protectant particles against receptive oxygen species (ROS). For instance, Myricetin and Quercetin, two flavonoids, were read for their expected enemy of diabetic action. The outcomes showed that these mixtures had powerless antidiabetic movement as displayed by their high portions in correlation with market drugs w^[52-53] [54]

Hesperidin –

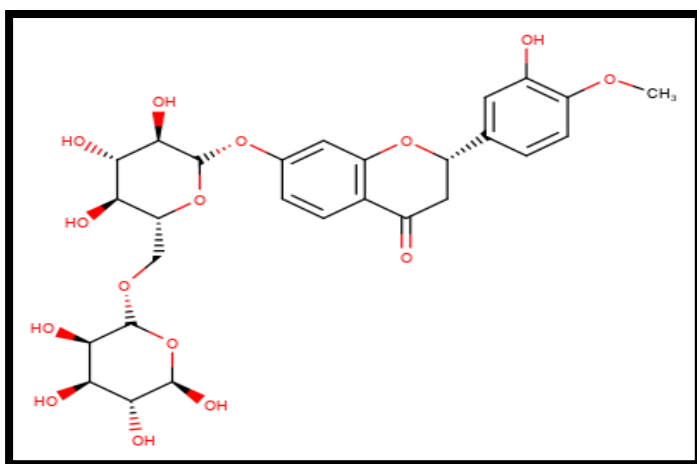


Fig 26: HESPERIDIN

Molecular Base: $C_{28}H_{34}O_{15}$

Molar weight: 610.1898 g / mol

Hesperidin is a flavanone glycoside found in aloe vera gel, Aloe vera L. (Aloe barbadensis) - Aloe barbadensis Mill. syn. A. vera (L.) Burm. f. (Barbados aloe, cape aloe) is referred to in Saudi Arabia as 'Sabar'. is viewed as viable in skin inflammation. Numerous dynamic fixings including aloesin, aloemodin, acemannan, aloeride, methylchromones, flavonoids, saponin, amino acids, nutrients, and minerals are recognized in the inward leaf gel. [14,15]

A. Vera has calming, cell reinforcement, antimicrobial, anticancer, boosting properties and hypoglycaemic properties. It is customarily used to treat numerous diseases. It is utilized remotely in the treatment of ulcers, bothersome skin and dermatitis.[16,17]

New aloe vera gel altogether decreased serious irritation in rodents (paw edema brought about via carrageenin), despite the fact that it didn't add to ongoing aggravation. Catalysts, carbs and sterols add to the calming movement of aloe juice. [13,12]



Fig 27: HESPERIDIN-Sources

Curcumin, Desmethoxycurcumin, Curcumol, Germacrone-

These are the flavonoids found in the rhizomes of *curcuma longa*, i.e., turmeric.[20]Turmeric develops woodland in the timberlands of Southeast and Southeast Asia. It has been utilized in Asia for millennia and is a significant segment of the Siddha tree. It was first utilized as a color and afterward for its restorative properties.[21]It has cell reinforcement, mitigating, antiviral, antibacterial and sterile. [22]The dynamic compound curcumin ought to have numerous natural impacts including mitigating, cancer prevention agent, antitumor, antibacterial and antiviral, showing its restorative potential.23 It is regularly utilized by people to treat dermatitis. It appears to be that the dynamic fixing curcumin present in turmeric has calming and bactericidal properties, which might be useful in treating dermatitis related skin irritation. The mending impact of turmeric is expected to polyphenolic curcuminoids including curcumin I, curcumin II, and curcumin III.[19]



fig 28: Curcumin-Sources

Antioxidant Activity of Curcumin-

Curcumin is known to secure biomembranes against peroxidative cell film harm (free-radical chain response). The restraint of peroxidation by curcumin is fundamentally ascribed to the searching of the receptive free extremists associated with the peroxidation. Theoretical estimations have shown that the enol type of curcumin is more steady than the keto structure and the BDE of the phenolic O-H security is essentially lower than that of the focal O-H, suggesting that the hydrogen atom extraction happens at the phenolic bunch. Litwinienko and Ingold as of late proposed the successive proton misfortune electron move hypothesis (SPLET) in ionizing solvents and H-Atom Transfer (HAT) instrument in non-ionizing solvents.^[55]

Apigenin, Cosmosiin, Hyperoside, Isoquercitrin-

These are the flavonoids found in the bloom of *Matricaria Chamomila*. *Matricaria chamomilla* L., otherwise called chamomile, is a yearly plant. It is a notable and broadly utilized restorative spice. *M. chamomilla*, an individual from the Asteraceae family, is one of the most seasoned therapeutic plants, generally utilized worldwide for an assortment of recuperating properties. The survey analyzes the proof base for the impacts of chamomile skin. [24] It has been discovered to be successful in treating wounds and aggravation of the skin, because of hypersensitive responses, atopic dermatitis and skin inflammation. Blossoms are utilized to make bits of tea and water, pills and tablets. It is applied to the skin as a balm or cream. Arrangements contain at least one equations and I

am answerable for securing human skin or shielding body cells from oxidative pressure, i.e., from harm to revolutionaries, for example They are additionally used to diminish legitimate maturing of the skin.^[26]



fig 29: APIGENIN-Sources

The primary motivation behind the current creation is hence the utilization of at least one mixtures as a functioning fixing to shield themselves from oxidative pressure. Additionally, the development intends to utilize at least one mixtures to forestall skin maturing. The synthetic substances seem to have against hypersensitive, mitigating, calming and hostile to disturbing properties and are in this way utilized as a treatment or treatment to forestall sensitivities, aggravation and bothering, particularly on the skin. In the event that the mixtures to be utilized by the innovation have free hydroxyl gatherings, and, notwithstanding the properties portrayed, go about as a cancer prevention agent and/or a solid engineered. Game plans with light-security properties are liked, containing in any event one part, described by at any rate one of the R 1 to R 3 revolutionaries being OH, ideally at any rate one of the R 1 or R 2 extremists being OH.

2.3 SUMMARY OF FLAVONOIDS-

FLAVONOID	NATURAL _i SOURCE
Kaempferol	Edible plants
Tiliroside	Plants of the genera Althaea, Aristolochia, Helianthemum, Lindera, Magnolia, Platanus, Potentilla, Quercus, Rosa, Sida, Sorbus or potentially Tilia.
Hesperidin	Aloe vera gel, Aloe vera L. (Aloe barbadensis) – Aloe barbadensis Mill. Syn. A. Vera (L.) Burm. F. (Barbados aloe, cape alo
Curcumin, Demethoxycurcumin, Curcumol,	Curcuma longs, i.e., turmeric.

Germacrone	
Apigenin, Cosmosiin, Hyperoside, Isoquercitrin	Flower of <i>matricaria chamomila</i>

Table 4: summary of flavonoids

2.4 PUBLISHED PATENTS-[8]

PATENT NUMBER	PUBLICATION DATE	TITLE
GB9104286D0	1991-04-17	Pharmaceutical compositions for the treatment of skin disorders
JPH06100584A	1994-04-12	New flavonoid glycoside
JP3839502B2	2006-11-01	Eczema / dermatitis group treatment
GB2291347A	1996-01-24	Pharmaceutical compositions comprising extracts of Chinese herbs
DE4444238A1	1996-06-20	Cosmetic or dermatological drug combinations of cinnamic acid derivatives and flavone glycosides
DE19544905A1	1997-06-05	Preparation of plant extracts
FR2778663B1	2001-05-18	Novel esters of flavonoids, their use in cosmetics, dermo pharmacy, pharmacy and agri-food
KR100675998B1	2007-01-29	Compositions comprising a mixture of bioflavonols
JP2002529090A	2002-09-10	Chemokine β -7

Table 5: Patent citations

CHAPTER 3

MOLECULAR DOCKING USING AUTODOCK VINA

AutoDock Vina employ for Docking protein1FQ3 (DOI: 10.2210/pdb1FQ3/pdb) inhibition of action associated in Eczema.

We demonstrate docking with the crystal structure of human granzyme B i.e, the 1FQ3 protein ,performing all procedure via using AutoDock vina and make possibilities of compound enlist associated to overcome or prevent the action of Eczema

Preparation of ligand and macromolecule

1. Collection of compounds from PubChem database[59]

Collection of compounds from PubChem includes are Kaempferol[PubChem CID 5280863] ,Tiliroside[Compound CID: 5320686] ,Hesperdin[Compound CID: 10621],Curcumin[PubChem:969516],Apigenin[PubChem:5280443],Isoquercitrin[PubChem:5280804]

2. Preparation drug molecule and protein structure

Drug molecule prepare by the following steps are includes such as ligand convert into 3D structure with explicit Hydrogen and optimized with energy to reduce the torsion and make flexible with different model of structure generation.

Protein molecule preparation via using ADT toolwith optimized all parameters with target selective chain and amino acids in given protein molecule and further performed the AutoDock Vina to final complex result of docking.[60]

POST DOCKING ANALYSIS

Visualization of Docking results via using PyMol 2.4.1(64 bit) and predict the best approaches compounds list on the basis of score and binding interaction.[61]

Ligand 1: Kaempferol

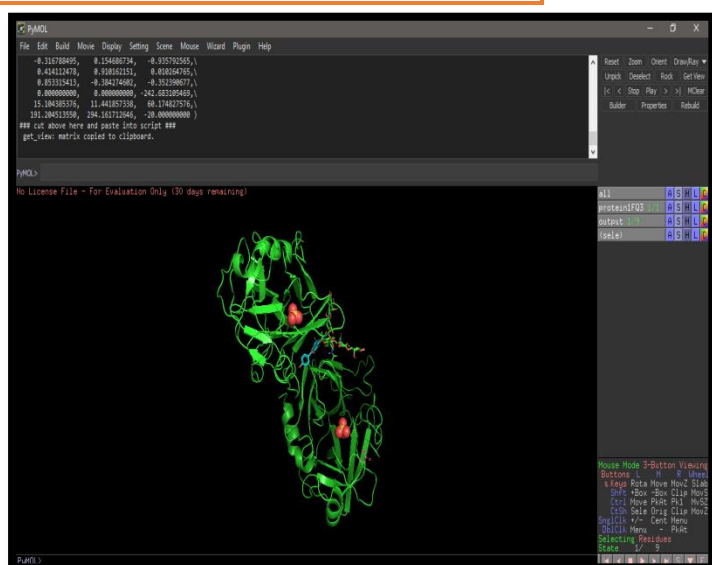
PubChem CID 5280863

mode	affinity	dist from best mode
------	----------	---------------------

	(kcal/mol)	rmsdl.b.	rmsdu.b.
--	------------	----------	----------

-----+-----+-----+-----

1	-9.0	0.000	0.000
2	-8.6	3.308	5.072
3	-8.5	2.559	3.302
4	-8.4	3.746	6.352
5	-8.4	3.438	6.480
6	-7.9	1.819	6.651
7	-7.9	3.677	6.549
8	-7.6	3.383	5.065
9	-7.3	4.582	6.338



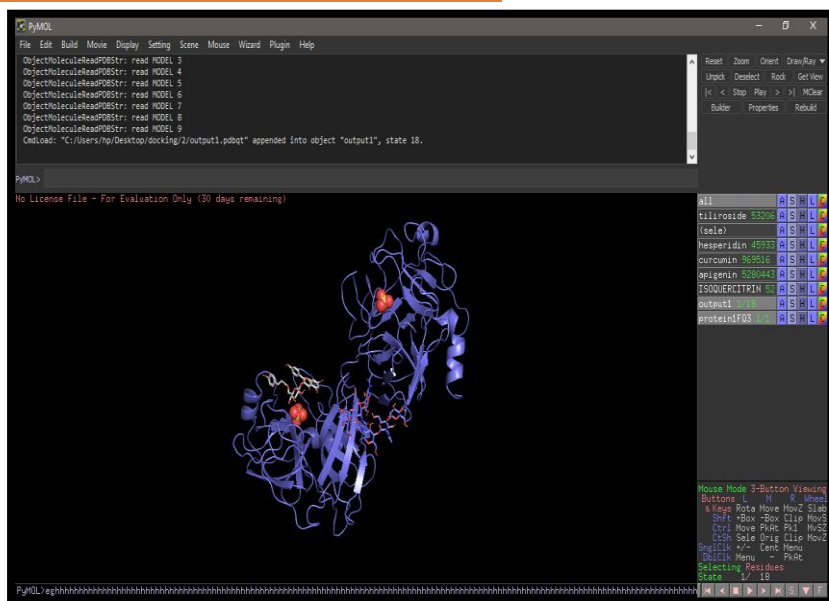
Ligand 2: Tiliroside

Compound CID: 5320686

mode	affinity	dist from best	mode
	(kcal/mol)	rmsdl.b.	rmsdu.b.
1	-8.7	0.000	0.000
2	-8.5	1.533	2.298
3	-8.3	5.621	9.436
4	-8.0	23.211	26.998

5	-8.0	1.734	9.232
6	-7.9	20.587	27.703
7	-7.9	22.336	26.803
8	-7.8	20.855	27.071
9	-7.8	22.259	26.255

Writing output ... done.

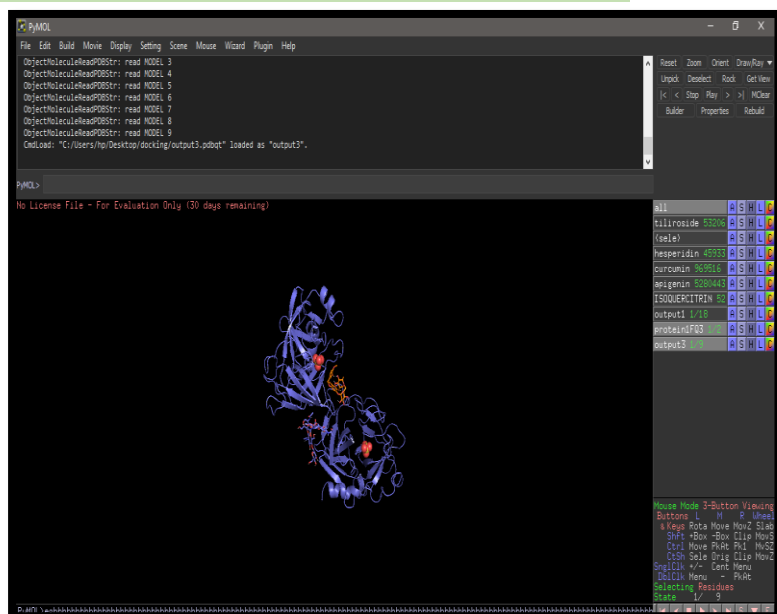


Ligand 3: Hesperdin

Compound CID: 10621

mode	affinity	dist from best mode	
	(kcal/mol)	rmsdl.b.	rmsdu.b.
1	-7.6	0.000	0.000
2	-7.3	9.552	13.751
3	-7.3	1.928	7.968
4	-7.2	6.407	11.746

5	-7.0	7.737	12.902
6	-6.9	16.915	21.030
7	-6.9	3.442	8.592
8	-6.8	15.337	19.799
9	-6.8	4.010	10.266
Writing output ... done.			

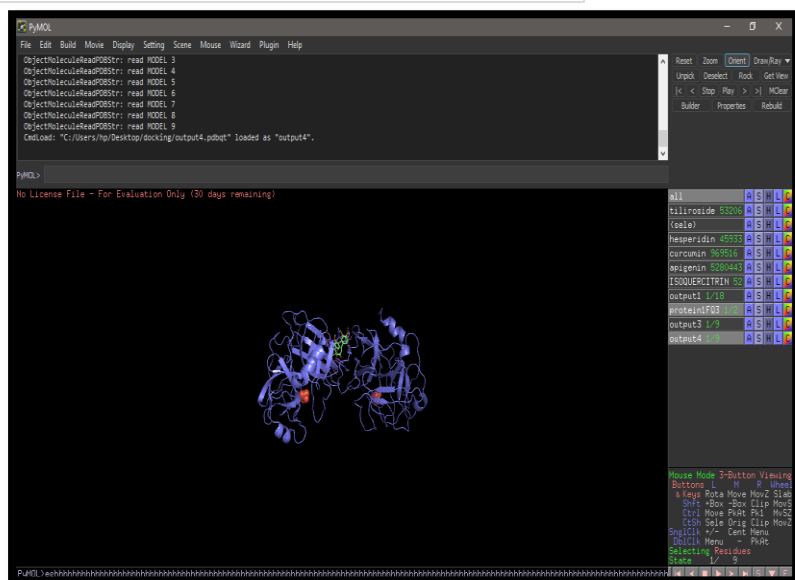


Ligand 4: Curcumin

PubChem: 969516

mode	affinity	dist from best mode	
	(kcal/mol)	rmsdl.b.	rmsdu.b.
-----+-----+-----+-----			
1	-8.2	0.000	0.000
2	-7.2	4.143	9.583
3	-6.7	11.376	14.677
4	-6.5	14.240	17.366
5	-6.5	24.836	29.402

6	-6.4	26.765	30.860
7	-6.4	23.685	28.233
8	-6.3	13.915	16.953
9	-6.3	12.669	16.768
Writing output ... done.			

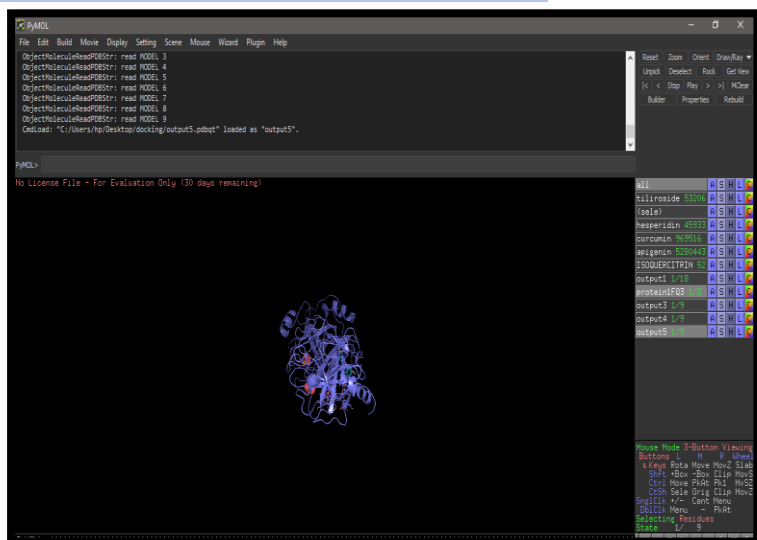


Ligand 5: Apigenin

[PubChem:5280443](#)

mode	affinity	dist from best mode	
	(kcal/mol)	rmsdl.b.	rmsdu.b.
1	-8.9	0.000	0.000
2	-8.4	3.344	4.918
3	-8.2	2.380	2.908

4	-8.1	3.555	6.510
5	-7.7	3.434	5.116
6	-7.7	4.432	6.115
7	-7.5	8.488	13.712
8	-7.5	26.518	29.139
9	-7.1	26.215	29.019
Writing output ... done.			

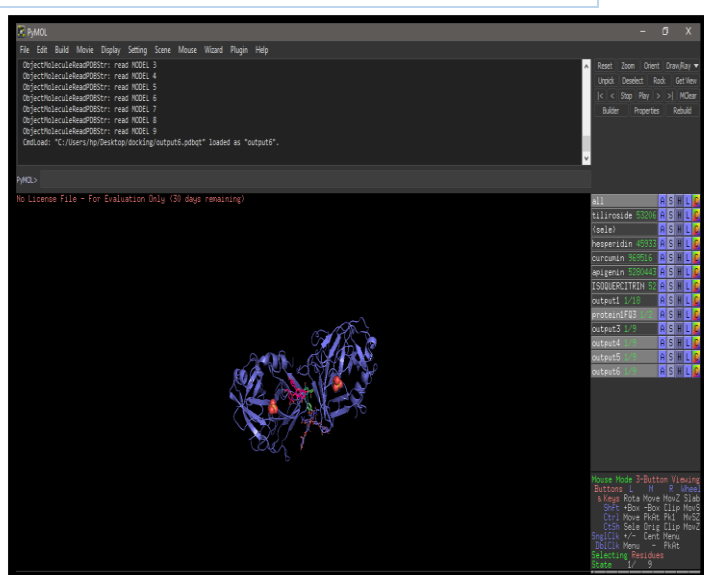


Ligand 6: Isoquertricin

PubChem:5280804

mode	affinity	dist from best mode	
	(kcal/mol)	rmsdl.b.	rmsdu.b.
-----+-----+-----+-----			
1	-7.2	0.000	0.000
2	-7.0	17.100	20.727

3	-6.6	7.796	10.469
4	-6.5	5.151	7.553
5	-6.5	13.639	16.746
6	-6.5	14.280	17.546
7	-6.5	18.825	21.973
8	-6.4	18.049	22.096
9	-6.4	3.887	7.907
Writing output ... done.			



CHAPTER 4

MARKET SURVEY ON VARIOUS FLAVONOID DERIVATIVES USED FOR THE TREATMENT OF ECZEMA

4.1 Objectives-

The survey is conducted to determine the number of cases found of Eczema and go through the number of patients and the commonly prescribed medicines for the disease that includes flavonoids as their component.

4.2 Survey Questions-

Flavonoid derivatives used for the treatment of eczema

I am a 4th year, Bachelors of Pharmacy student from Galgotias University, Greater Noida. Please help me complete my project by filling this survey form.

Name *

Short answer text

Profession

Doctor

Pharmacist

Other...

Age Group *

below 18

18-24

25-40

41-60

above 60

Have you heard about Eczema/Atopic Dermatitis? *

Yes

No

Maybe

If yes, have you suffered from the disease or someone known has suffered?

- Yes
- No
- Maybe

From the above question,if yes ,what were the common problems faced?

- itchy bumps on skin
- scaly skin
- blisters
- red burns
- stinginess

If a doctor, what medicines did you prescribe for eczema patients?

Short answer text
.....

If a pharmacist, what medicines were mostly sold for eczema?

Short answer text
.....

Have you heard about flavanoids being used for treatment of eczema?

- Yes
- No
- Maybe

If yes, which of the following flavanoids did you hear of?

- Kaempferol
- Tillroside
- Hesperidin
- Curcumin
- Demethoxycurcumin
- Curcumol
- Germacrone
- Apigenin
- Cosmosiin
- Hyperoside
- Isoquercitrin

How often do you witness Eczema patients?

daily

weekly

monthly

yearly

How much time does this disease needs to be cured?

< 1 week

week

15 days

month

> a month

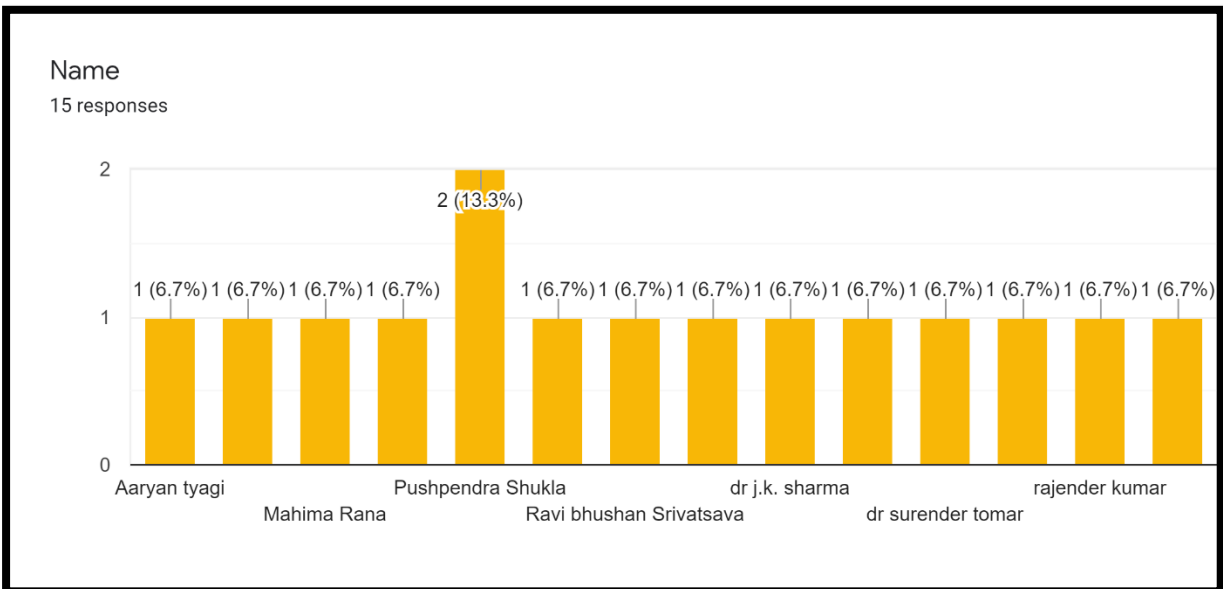
Who are the most suffered patients of Eczema?

Male

Female

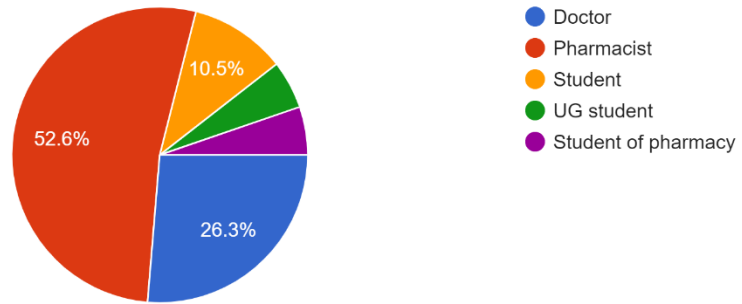
Prefer not to say

4.3 Survey Results-



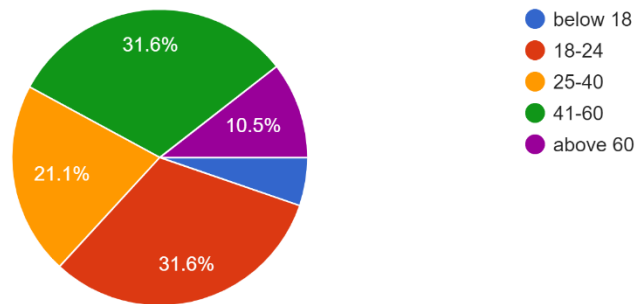
Profession

19 responses



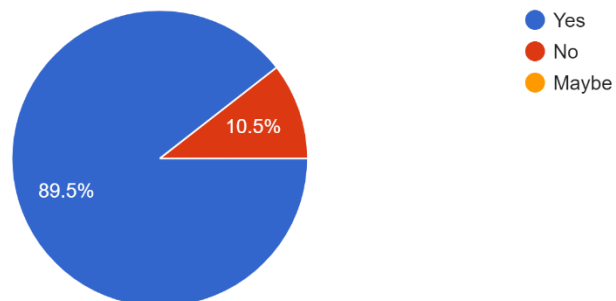
Age Group

19 responses



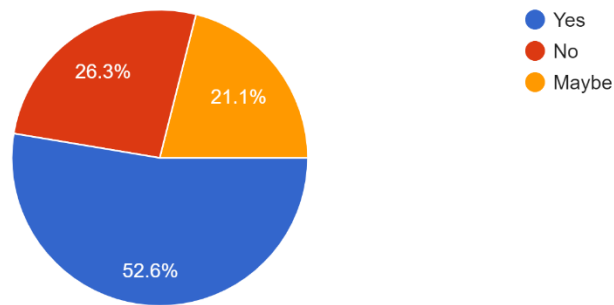
Have you heard about Eczema/Atopic Dermatitis?

19 responses



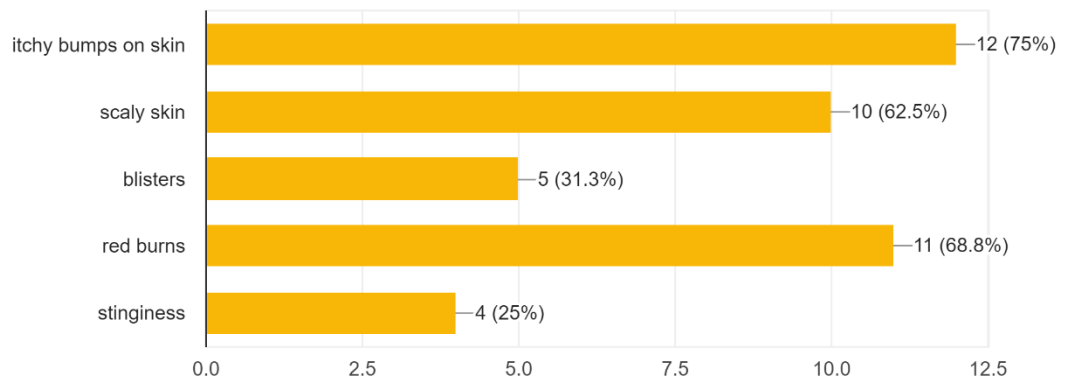
If yes, have you suffered from the disease or someone known has suffered?

19 responses



From the above question,if yes ,what were the common problems faced?

16 responses



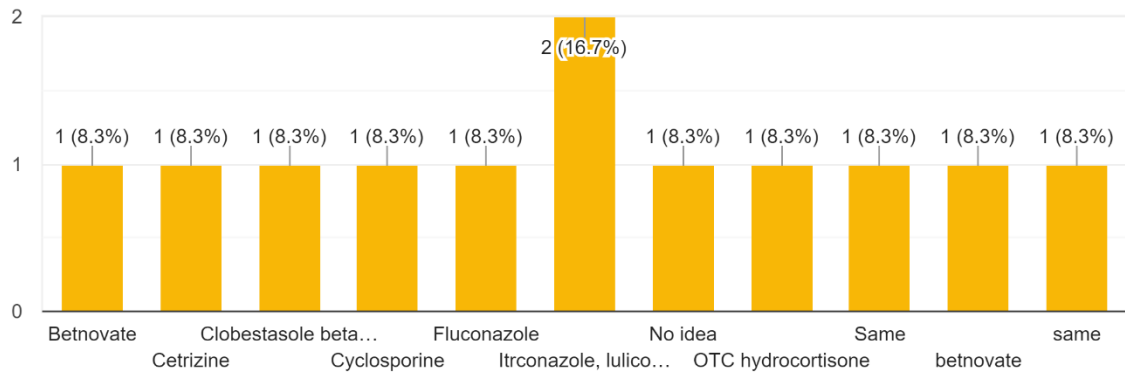
If a doctor, what medicines did you prescribe for eczema patients?

11 responses

- Antihistamines
- Antibiotic
- Fexofenadine , Loratadine , amoxicillin , cephalexin
- avil,levocetriine,allegra,candid b lotion
- Terbest 250,alespan, atarest, fluconazole, curanest, pernox 2.5
- Anti allergic & topical cream
- No idea
- antihistamine
- loratadine

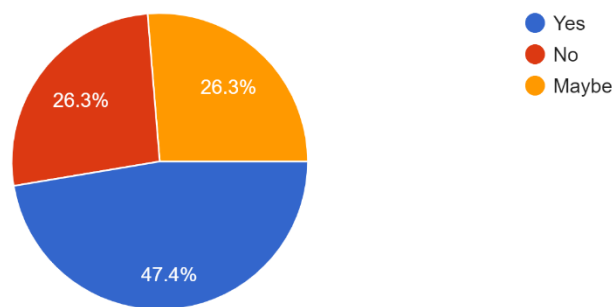
If a pharmacist, what medicines were mostly sold for eczema?

12 responses



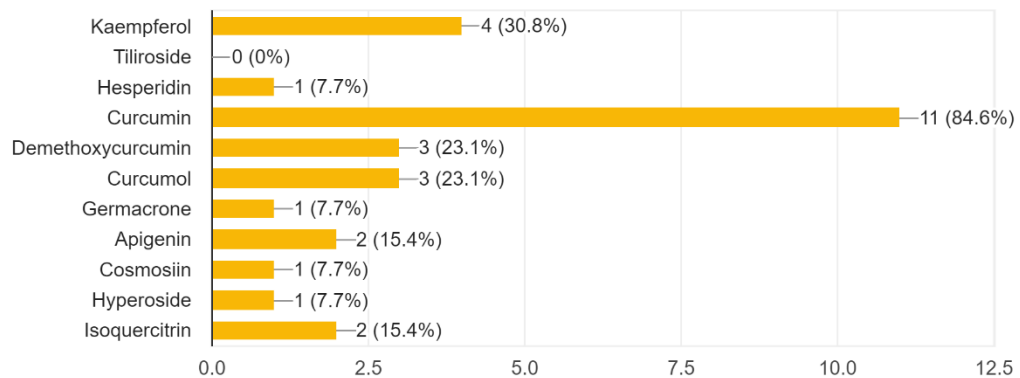
Have you heard about flavanoids being used for treatment of eczema?

19 responses



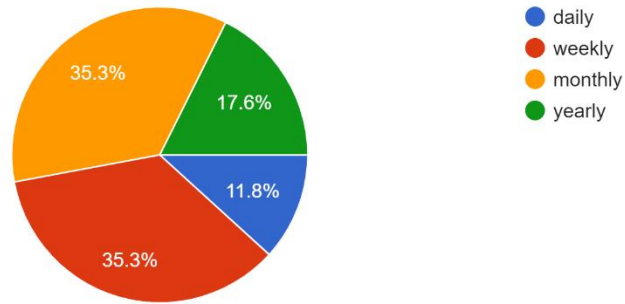
If yes, which of the following flavanoids did you hear of?

13 responses



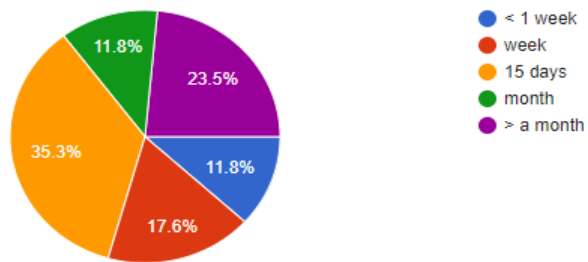
How often do you witness Eczema patients?

17 responses



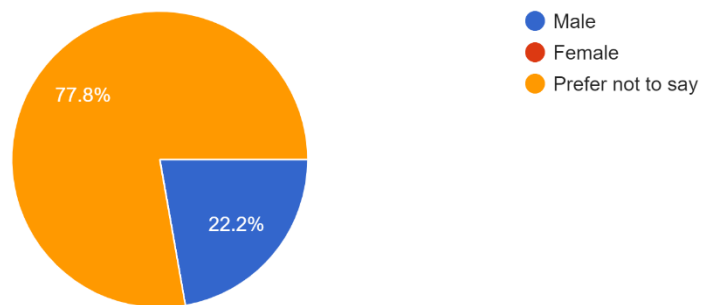
How much time does this disease needs to be cured?

17 responses



Who are the most suffered patients of Eczema?

18 responses



4.4 Results and Discussion-

SNO.	QUESTION	DISCUSSION
1	Profession	52.6% of the survey has been completed by pharmacists.
2	Age Group	31.6% people are from the age group 18-24 and 41-60
3	Have you heard about Eczema/Atopic Dermatitis?	89.5% people voted Yes
4	If yes, have you suffered from the disease or someone known has suffered?	52.6% people voted Yes
5	From the above question,if yes ,what were the common problems faced?	75% people have faced itchy bumps on skin.
6	If a doctor, what medicines did you prescribe for eczema patients?	Most of them have prescribed antibiotics,antihistamines and anti allergics
7	If a pharmacist, what medicines were mostly sold for eczema?	16.7% people have voted for itraconazole and luliconazole
8	Have you heard about flavanoids being used for treatment of eczema?	47.4% people voted Yes
9	If yes, which of the following flavanoids did you hear of?	84.6% people have voted for curcumin
10	How often do you witness Eczema patients?	35.3% people voted for weekly and monthly
11	How much time does this	35.3% people voted for 15 days

	disease needs to be cured?	
12	Who are the most suffered patients of Eczema?	35.3% people voted for prefer not to say.

CONCLUSION-

Regular assets have incredible potential for treating different afflictions. Numerous individuals all throughout the planet utilize different plant items to treat skin issues. These spices are a rich wellspring of dynamic fixings and can be protected and costly to treat different skin afflictions. Irritation is a mind boggling measure, needed by the resistant framework. Over the top creation by some consuming middle people can cause persistent illnesses. Plant youthful things can have a mitigating activity that influences different phases of the provocative interaction. They forestall the development of cytokines and eicosanoids, stop the spread of irritation in any case, and decrease skin aggravation, tingling or exorbitant discharge. Albeit these spices are by and large protected to use on the skin, a few group may create sensitivities or hypersensitivities to specific plants or flavonoids or different supplements in plants that can cause disturbing contact dermatitis or sensitivities. Along these lines, we need to continually test new fixings prior to joining them into a healthy skin system.

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