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Review Article

Therapeutic Options and Drug Delivery System & Potential Herbal Molecules Forvitiligo Therapy

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Abstract:
Vitiligo is a condition in which the skin start to lose its pigmentation that appear to be white patches on the skin, the mechanism of vitiligo is still under investigation but some of the hypothesis suggest that it is an autoimmune disease in which amount of melanine is reduced in certain areas of the skin.Various biomarkers have been identified by the scientists that help in the assessment of this disease which further help in the treatment of this disease. Many herbal drugs are proven to be effective in the treatment of vitiligo for example; Ashwagandha, Black Cumin, Barberry Root etc. many of the herbal products of these and other plants are available in the market like Anti-leucoderma oil, Ayurhealthline capsules, Ayurhealthline cream, Pigmento cream.
Key words: Vitiligo, Skin, Treatment, Drug Delivery system, Potential molecules.

Introduction

Skin which is the largest organ of the body suffer from numerous disease/disorders one of those which affect the human population widely is vitiligo; is a condition in which silvery white patches develop over the skin surface that can be categorize on the baseof the pattern in which they are appearing on the body, the two main class are segmental and non-segmental. It affects almost 0.5% to 1% of the total world population. The exact mechanism in the occurrence of these white patches is still a matter of debate,but some

theories are suggested that it may occur due to some of the following reason – genetic defects, oxidative stress, and the widely accepted theory is the auto-immunity aaccording to which the melanin producing cells melanocytes are targeted and destroyed by the body own self defense system resulting in the loss of the pigment from the skin. Various other factors that contribute in the occurrence of these white patches are weaker occurrence of E- Cadherin and Discoidin Domain Receptor (DDR1), FOXO3A protein variation can also might be a risk factor. Various synthetic drugs are used in the treatment of this disorder e.g.-Methoxsalen, psoralen, tacrolimus, etc. but these synthetic drugs comes with some potential side effects like contact dermatitis, rashes, inflammation, etc. herbal drugs has potential to treat this disorder without producing potential side effects many herbal drugs are used in the treatment of vitiligo like- khella, brahmi, shankhpushpi, ashwagandha, black cumin, barberry root, etc. In this review article we are studying the potential of some of these herbal drugs and other synthetic drugs and their different kinds of formulations that are available in the market like capsules, oils, creams, tablets, ointments, etc. for the treatment of vitiligo.

Vitiligo

Vitiligo is the gradual loss in the number of melanocytes from several areas of skin resulting in psychological and social discomfort **[33,34].**The result of this loss is the appearance of silvery white patches or macules**[32]** over the skin, the most likely parts affected by this infirmity are wrists, axillae, perioral, hands, anogenital skin etc.**[1].** Though this ailment is considered to be autoimmune ailment but it does not reach the systemic circulation and do not get involved other organs as in the other ailments **[20].** There is no illustration of the pattern of which race is more susceptible because it affects almost all races and geographic area with a prevalence of 0.3 to 0.5 % **[17,35].** This ailment can begin almost at any stage of life but 50% of vitiligo cases are found to be of age group of 20 to 25 years **[36].** Various theories about the appearance of this ailment has been suggested by scientists but the most widely acknowledged theories are; auto-cytotoxic hypothesis, neural hypothesis, autoimmune hypothesis, and oxidative stress theory **[22].** In vitiligo there are 2 possibilities i.e.,either melaninsynthesizing melanocytes are absent or melanocytes associated protein are not present (example MelanaA or S 100 or tyrosinase)**[1].**

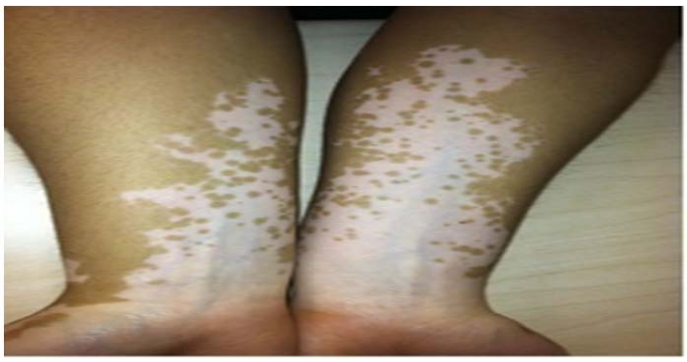


Figure 1: Figure showing a typical case of generalized vitiligo[16].

Classification

The vitiligo ailment can be categories on the basis of experimental knowledge into three main categories i.e., segmental vitiligo, non segmentalvitiligo, mixed vitiligo,

Non-segmental- The main characteristic of non segmentalvitiligo is that depigmentation of the skin show symmetry in the pattern **[3,16]**. In other words it can be said that it appeared either side of body **[19]**. Among all the types non segmental vitiligo are the usual type that occurs

in almost 80% to 90% of the total vitiligo cases **[33]**.

a) Generalisedvitiligo: The generalisedvitiligo can be explained as acquired, non contagious, ailment **[58,60]** that can be characterize by the appearance of symmetrical macules **[3,14]** over the skin that mainly appeared at hands, feet, fingers, face and the area that area of skin that suffered from any trauma/damage **[61].** This type considered to be the most usual type of the vitiligo**[59,63]** and can also be observed in close relative of the individual affected from this disease **[28]**.

b) Universal vitiligo: This is type of vitiligo that covers the greatest portion of the skin surface (almost whole body 80-90%) **[61]**. In other words approximately entire depigmentation. The word universal vitiligo usually used to refer the condition in which non-segmental type advances and cause depigmentation of almost entires body skin **[3,14,62]**.

c) Acrofacialvitiligo: The person affectes from acrofacialvitiligo usually have depigmentation of areas namely, face, head, feet, hands, with preference of preioral region and margin of digits **[3,21,61]**.

Segmental Vitiligo: This type of pattern of macules is much more different from other types and subtypes of macules in term of etiology, spreading pattern and size and shape, but this type of vitiligo respond easily toward topical therapy **[3]** also various experiment shows its relation with immune response **[28].**As per the experimental evidence this type is characterize by its property of the presence of macules at one, two and/or multiple segments **[19]** out of which unisegmental type considered to be the usual form that appeared in population **[61]**.

a) **Uni/pluri Segmental Vitiligo:** It is the subtype of segmental vitiligo that is characterize by dermatomal division. These subtypes most frequently affects childrens and progression of these subtypes stops at mildness **[14, 16]**.

b) **Focal Vitiligo**: The focal subtype characterize by minor, solitary, silvery white patches, another characteristic of this subtype is that it does not progress to become non-segmental even after the time span of 1-2 years **[62]**. This subtype also affects children's most frequently **[3,19]**.

c) **Mucosal Vitiligo**: This is the subtype of vitiligo that is characterize based on the property to affects mainly oral and/or genital mucosa membrane **[3,61,62]**.

Mixed Vitiligo: This is the category of vitiligo that does not fall in any of the above mentioned category, rather both non-segmental and segmental occur simultaneously in the affected individual **[14,61]**.

Pathogenesis

1) Autoimmunity hypothesis: This autoimmunity assumption is most widely and commonly acknowledged theory that explain the mechanism of pathogenesis of non segmentalvitiligo, this assumption involves autoimmune/Inflammatory mechanism affect the melanin producing melanocytes that are present in the skin**[19].** Melanocytes are prone to immunological cytotoxicity and toxicity caused by reactive oxygen species because the antioxidant defense gotten weaker**[22].** Most of the experimental illustration support autoimmune theory because of antibodies present at the margin of macules**[1].** Circulating antimelanocyte antibodies (antityrosinase related protein-1, antityrosinase, antidopachrometautomers) was seems to appear and are directed toward melanocytes, another vitiligo related antibodies targets were detected (Lamin A, MCHR-1PM-17, SOX-19, SOZ-10, tyrosine hydroxylase)**[16].** The appearance of skin homing cytotoxic T-cells in circulation**[18,19]** The infiltrate of border of macules were found to have macrophage and activated cytotoxic T cells**.** These dynamic T-

cells aims the melanocytes specific antigen (melanA(MART-1), gp-100(Pmel 17) &tyrosinase)**[16].** Also these T-cells seems to be present in lesional skin, most of theinflammation appear within the leading edges of macules. Infiltrate of these macules involved CD8+ and also dendritic cells, CD 4+ T cells and macrophages. It is hypothesized that T cells are actively directed toward melanocytes **[19].**

2) Oxidative stress hypothesis: In various experiments scientists has found that the oxidative stress is one of leading factor that cause vitiligobecause in their findings they reported that an individual affected from this ailment show decrease in antioxidant defense mechanism activity on the other hands several oxidative stress markers found to be increased that indicate the involvement of oxidative stress, markers such as malondialdehyde, selenium, lipid peroxidation**.** The activity of different isoforms of superoxide dismutase(SOD) i.e., SOD1, SOD2, SOD3 found to be increased drastically in individuals affected from this ailment, SOD are enzymes that modify pro-oxidant superoxide into H_2O_2**[23,38]**. The oxidative stress appears in situation where the production of reactive oxygen species exceeds far then the detoxification capability of the cell. In vitiligo affected individual several growth factors found to be in higher concentration then the normal levels like TNF-α, IL-6, basic fibroblast growth factor etc, these growth factors were reported to be responsible for making cell produce reactive oxygen species **[49]**. Catalase is an enzyme that nullify the H_2O_2 by converting it into O_2 and H_2Othus detoxify it, but in case vitiligo patients, reduced activity of this enzyme were observed **[53,54]**. In other experiment scientists observed that FOXO3A is a gene that isa gene that is responsible for the controlling the production of catalase, in vitiligo affected individual the scientists found the lower expression of this gene that directly affects the antioxidant defense machinery of the body **[6,55]**. The above theory of oxidative stress due to reduced catalase activity were supported by an experiment in which scientists isolated melanocytes from affected individual from affected and non affected area and from normal healthy individual, these melanocytes when cultured it was observed that melanocytes from affected individual both from affected and non-affected site unable to sustain in normal growth medium compared to these, melanocytes from normal healthy individual grow properly, scientists when modify the growth medium for affected individual melanocytes by adding catalase in the medium they observe that the affected individual melanocytes can grow properly in that modified medium this experiment support the hypothesis of oxidative stress **[56]**.

3) Neural hypothesis: Base of this assumption is the presence of an imbalance in the levels of adrenergic/cholinergic hormones in an individualaffected by this ailment**[22].**

4) Auto-toxic hypothesis: This assumption is basedon the excess production of toxic melanin metabolites that results in the auto-cytotoxicity **[22].**

5) Environmental factors: Several of environmental factors are responsible in the occurrence and progression of vitiligo several assumption has been made trying to explain the contribution of the environmental factor in vitiligo. In a study including some patient describe a form " occupational vitiligo or contact vitiligo", this study provide an insight about certain chemicals like aromatic or aliphatic derivatives of phenol association with vitiligo, the discoloration may be limited to the point of exposure or may spread **[19].**

6) Other factors causing vitiligo:

a) Epithelial Cadherin (E-cadherin)and Discoidin Domain Receptor-Tyrosine Kinase 1 [DDR1] are the two main proteins present in the basal layer of epidermis. It was observed that less occurrenceof these proteinscan be a provoking factor that results in the loss of

melanocytes in individual affected by this ailment **[5].**

b) Pro-inflammatory cytokines such as IL-1B,IL-6, IL-8, TNF-α are observed to be produces in excess in infiltrates of PBMC (Peripheral Blood Mononuclear Cells)from periphery of vitiligo macules of affected individual, this is proven from experiments that it might be aaggravating factor for vitiligo development. IL-10 is a sensitive gene which is susceptible to methylation is found to be hypermethylated in $CD4^+$ T-cells, in an experimental conducted by Zhao et al. it was observed that the enhancer region present in intron 4 of IL-10 posses eight CG pairs is hypermethylated in vitiligo affected individual. The study also shows that the change in methylation of DNA in $CD4^+$ T cells of vitiligo affected individual increase the chance occurrence and progression of vitiligo**[20].** Also the proteins named DNMT (DNA Methyl Transferase) and methyl DNA-binding domain proteins that includes MBD1, MBD3, MBD4 and MeCP2 were observed in excess they may be an aggravating cause of DNA hypermethylationand vitiligooccurrence and progression **[21].**

c) Several high level studies are able to explain the link between the vitiligo and associated gene more than 30 genes are suspected to be involved in the occurrence and progression of this ailment, name of some genes are; RERE, FOXD3, CD80, CLNK, TSLP, TYR, Chr11q21, GZMB, MC1R, FOXP3, T0B2. etc**[31].**

Biomarkers of Vitiligo

1) Plasmacytoid Dendritic Cells (pDCs): An excess amount of $CD123^+$ PDCs marker was found in the infiltrate of active macules present on the skin of affected individual**[23].**

2) NLRP1: Analysis at genetic level has provide a connection between NLRP1 vitiligo. NLRP1-Nucleotide-Binding Domain that is rich in lucin repeating unit and pyrin domain containing protein are the part of NLRP1 inflammasomes activation of which cause production of IL-1β and IL-18 **[23].**polymorphs rs2670660 and rs6502867 appeared to be involved with vitiligo**[30].**

3) T-Cells: The infiltrates of active macules of vitiligo affected skin showed increased level of CD3, CD4 and CD5 cells relative to stable the vitiligo**[24,25].**

4) Cytokines: With the help of experiments a positive relationship between the ailment vitiligo and increased level of IL-6, IL-8 **[39,40]** IL-17 was established similarly an increased in the number of IL-17R receptor was observed in active versus stable comparison**[26].**

5) Chemokines and Soluble CDs: CXL9 assumed to be an good biomarker presentin the fluid of suction blister fluid of active vitiligo macules with a specificity of 93% and sensitive of 100% **[27].** The level of CXCL12**[2]** in the serum which is a ligand of CXCR4 found to be higher in individual active vitiligo relative to the control.

6) Tregs: Tregs are the one which is responsible in the protection of body from autoimmune disorder in vitiligo affected individuals there level were observed relatively low then the normal person **[28,29].**

7) Antibodies: Experimental results showed that autoantibodies such as IgG were present in relatively higher concentration **[40]** indicating positive relationships in between the occurrence and progression of disease with these antibodies, in a similar but relatively small sized experiment IgG pigment cells specific antibodies were observed in 8/10 vitiligo active individual **[23].**

8) Oxidative Stress: Scientists have found from various experimentation that oxidative stress rise in vitiligo active individual **[38]** or in other words it can be said that the antioxidant

defense mechanism of the affected individuals falls below the safe level that prove its association with this ailment activity **[23].**

9) S100B: A protein name S100B approved in injured melanocytes which is considered to be a marker of melanocytes cytotoxicity in other words S100B value is increased in the active vitiligo indicating its association with vitiligo**[4].**

Current treatments

Currently a number of treatment are officially being used to treat vitiligo with a goal to increase the population of melanocytes in the vitiligo affected area to restore the normal pigment of skin in that area of body. The degree of treatment relies on various factors such as site of macules and to which extent they spread also which type of skin individual have, also the age, the encouragement to complete the therapy play an important role **[3].**

1) Corticosteroids therapy: They are considered to be the first and foremost treatment for vitiligo**[3,12].** The mode of action of these drugs are said to be the cellular and humoral immune response **[13].** There are certain side effects of these drug including atrophy, striae etc. **[52]** Example of these drugs are methotrexate, minocycline **[48]. A.Ayman et al** performed their research over 1% methotrexate gel in search of its effectiveness in the vitiligo therapy and reported that methotrexate gel can be a useful tool in the therapy of vitilgo**[64]**.**P. Davinder et al** in their study has shown that minocycline can be prove quite effective in the vitiligo therapy due to its effects on the oxidative stress and apoptosis which are considered to be the prime reason behind the occurrence of vitiligo**[67]**.

Marketed products of methotrexate

- METH gel (gel)
- Dermotrex gel (gel)
- Trexjoy (Cream)

Marketed products of minocycline

- MINOZ^{TM} 100 (Tablet)
- MINOZ OO 100 (Capsule)
- Minolin 50 (Tablet)

2) Phototherapy: Phototherapy is pioneer cure for vitiligo the mode of action of phototherapy is said to be the immunosuppressive action on T- lymphocytes **[3, 12].**

A) PUVA photochemotherapy

a. **Topical PUVA:** This therapy use psoralen which is applied topically **[7].** It is more effective and safe for children of age group of 2 years **[3].**

b. **Oral PUVA:** It is an option for those individuals which do not respond to the topical PUVA treatment, but it is not preferred for the patient who are younger than 12 year of age **[3].**

c. **Water bath PUVA:** This method involved the bathing of individual in psoralen mixed water for the absorption of this drug through skin after which the individual go through with a photo therapy session **[3, 12].**

3) Narrow band PUVA: This treatment also called as Tl-01 therapy, this treatment do not include the use of psoralen not orally nor topically, the wavelength used for the treatment is 311 nm **[3,12,13].** This therapy first used to treat psoriasis **[50].**

4) Auto-immune vitiligo T-cells: Separated T-cells; CD8 & CD4 **[16]** from the edges of macules are allow to multiply and developed in a condition that lack the functional T-regulatory cells. These cells then function as the inhibitor of immune system by making IL-10 and TGF β that stop autoimmunity **[3].**

5) Tissue graft: In this method the tissue from unaffected site is removed and inoculated inside the orifice formed at the affected site

using biopsy punch and protected with petrolatum gauze or adhesive tape **[3, 12].**This induce pigmentation in almost 77% of the cases **[51].**

6) Split thickness skin graft: In this method after acquiring a skin graft from an unaffected site is put to the dermabrades affected area with the help of dermatome **[3,12].**

7) Noncultured keratinocytes: In this, a suspension of cells that has melanocytes is prepared by the donor tissue after that with the help of nitrogen, blisters are developed on the affected site in which cellular suspension is contained and monitored forrepigmentation**[3,12].**

8) Fake tanning products: These are cosmetics products that gives off the look of natural skin color **[3].**

9) Pseudocatalase: Pseudocatalase helps in restoring the normal level of the catalase enzyme, that is responsible for the detoxification of the H_2O_2 , in research it was observed when applied topically in conjunction of phototherapy it produce satisfactory results **[13].S. Bakis-Petsoglou et al:** performed their experiment on finding the efficacy of pseudocatalase cream in conjuction with narrow band UVB for the treatment of vitiligo and concluded that when pseudocatalase used in solitary does not produce much effects but in conjuction of the phototherapy produce satisfactory effects **[65]**.

Marketed products of pseudocatalase

- VITILASE Cream (Cream)
- Pseudocatalasecosmeceutical cream (Cream)
- Acticatedpseudocatalse (Cream)

10) Vitamin D analogues: When PUVA and calcipotriol**[48]** used combindly they produce better effects in regaining the skin color and reduce the time required in the treatment **[3,13]. C. Chiaverini et al** in their study reveals that use of calcipotriol in solitary can not be a good option to be used in vitiligo therapy as it is not that effective alone **[66]**.

Marketed products of calcipotriol

- Pasitrex (Ointment)
- CALPSOR (Ointment)
- CALLOVE (Ointment)
- HEXIMAR (Ointment)

11) Calcineurin inhibitors: Tacrolimus,**[47]** a prepration of immunosuppressive macrolid FK560 **[3]** and Pimecrolimus are prove to be effective in both generalised and localized treatment of this ailment **[9,48]. M. Cavalie et al** in their study on tacrolimus provide an statement i.e., when tacrolimus 0.1% ointment applied twice weekly can help in the stoping of the progression of the vitiligo macules and helps in the repigmentation of the skin affected from this ailment **[69]**.

Marketed products of tacrolimus

- Tacroz Fort (ointment)
- Tacrolimus ointment 0.1% (Ointment)
- COSSRIM (ointment)

12) Natural treatment: As we all aware about that mother natureposses cure of almost all disease known by human, all that need is to explore, with this in mind several natural products are being investigated and are currently used in the treatment of vitiligo some of these are as follows.

a) Shankhapushpi: This plant possess the antioxidant activity that help in reducing the oxidative stress that is thought to be the one of the cause involved in the occurrenceand progression of the vitiligo**[14].**

b) Ashwagandha: This plant contain various phytoconstituents, among which Withaferin A possess antioxidant activity **[15]** and enhance proliferation of melanocytes and also possess immunomodulatory activity **[41,43],** thus help in treatment of vitiligo**[42].**

c) Khella- It belong to the family of carrot (umbelliferae), it contain khellin**[13]** which is its active constituent. It is used in various disorders such as abdominal cramps, painful mensturation, vitiligoetc**[9].O. Bernhardel et al** use khellin which is a phytoconstit of khella plant in vitiligo therapy in conjuction of phototherapy and concluded that khellin can be a good replacement of the psoralen in photochemotherapy of vitiligo**[69]**.

d) Marketed products of khellin

- Khellin 10:1 extract (Capsules)
- AmmiVisnaya cream (Cream)

e) PsoraleaCorylifolia: This plant contain psoralen and isopsoralen and furocumarine which helps in providing skin its natural colour**[8,42].**Psoralen in I.P. is categorized as topical pigmenting agent **[57]. Pearl E. et al** in their experiment use psoralen in vitiligo therapy conclude that psoralen is effective in the treatment of the vitiligo and reduce the chances of reoccurrence of the white macules **[68]**.

Marketed products of psoralen

- Psorlen NH (Capsules)
- Verdura (Cream)
- Psoralen ointment (Ointment)

f) Pipernigrum and piperlongum: Piper nigrum and Piper longum both of these plant contain piperine as an active phytoconstituent which possess antioxidant activity **[41,43,44]** and also it enhance the growth of human melanocytes **[46].**

Marketed products of pepper

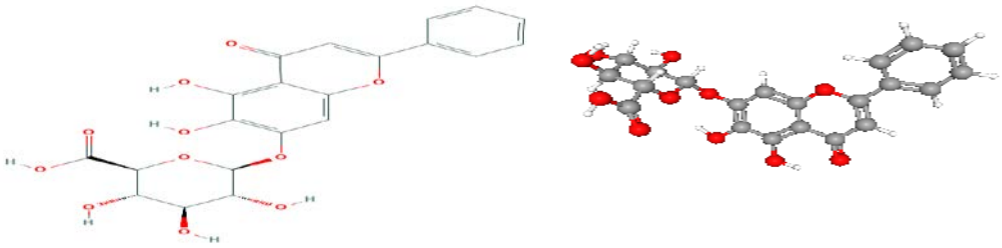
- Organic black pepper (oil)
- Black pepper essential oil
- Coenzyme Q10

Other herbal marketed products for vitiligo treatment

- Pigmento cream
- Ayurhealthline cream
- Ayurhealthline capsules
- Kalawallavitiligo dietary supplement
- Ayurhealthline anti-vitiligo kit
- Dermablend cover cream
- Anti-leucoderma oil
- Pigmento tablet

Molecules having potential to treat vitiligo:

Jingjing Ma et.al, performed their experiment to find out the potential of baicalein (**Figure 2**) which is an flavone obtained from Scutellariabaicalensis, to protect melanocytes in individual suffer from vitiligo and observed that baicalein shielded the melanocytes from oxidative stress by stimulating Nf-E2 related factor 2 [NrF2] signaling pathway thus proving its effectiveness in vitiligo therapy**[71]**

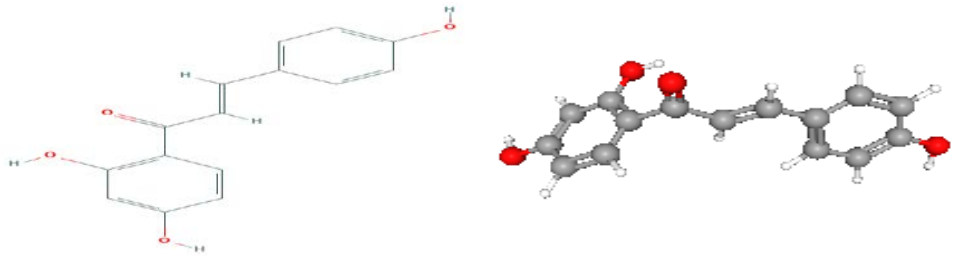


(a) (b)

Figure 2: (a) 2D structure and (b) 3D structure of baicalein.

Jinpeng LV et.al,they explore the potential of isoliquiritigenin (**Figure 3**) i.e., a flavonoid obtained from Glycyrrhizaglabraroots; in their study they observed that isoliquiritigenin hinder melanogenesis by reducing tyrosinase activity in the melanocytic cells of human thus it may be used in case of universal vitiligo in which

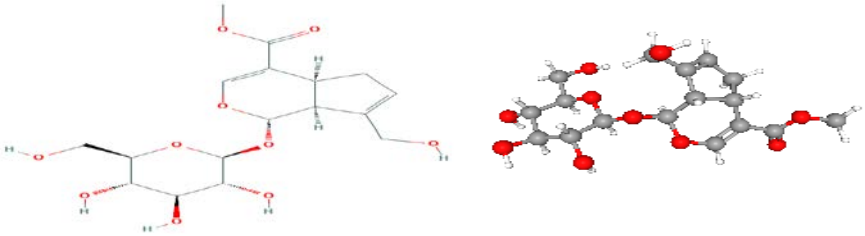
only fewer spots of melainated skin remains, treatment with isoliquiritigenin helps in removal of those spots and provide skin an even tone**[72]**.



(a) (b)

Figure 3: (a) 2D structure and (b) 3D structure of isoliquiritigenin.

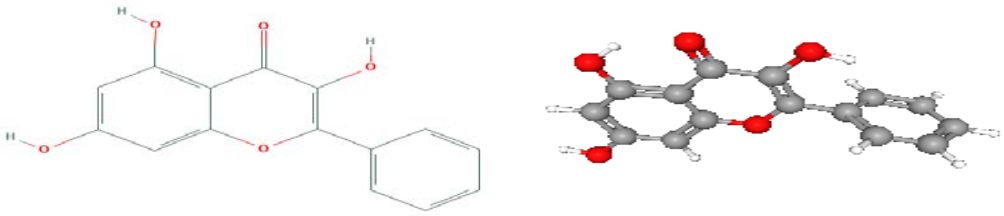
Wen Jun Lan et.al, in their study to find a potential vitiligo treatment, they experimented on geniposide (**Figure 4**) which is airidoid glycoside obtained from fruits of Gardenia jasminosides Ellis. In their findings they observed that stem cells factor from keratinocytes recognize & activates its receptors C-kit presents on melanocytes to enhance melanogenesis. They observed that geniposide increase melanogenesis by activating stem cell factor/C-kit signaling**[73]**.



(a) (b)

Figure 4: (a) 2D structure and (b) 3D structure of geniposide.

Shi-xiaHuo et.al, in their study over galangin (**Figure 5**) which is a major phytoconstituent of Alpiniaofficinarumand observed that galangin have potent redical scavenging and antioxidant properties and can help in elevating the levels of tyrosinase, which is an enzyme required by melanocytes for the production of melanin, thus galangin can help in vitiligo therapy**[74]**.



(a) (b)

Figure 5: (a) 2D structure and (b) 3D structure of galangin.

Jing-Hua Wang et.al, in their study over bavachinin (**Figure 6**) which is an flavonoid obtained from Psoroleacoryfolia, they observed that bavachinin shows higher inhibitory effects towards melanin synthesis &tyrosinase activity when given in dose of 10μmol/L it inhibits expression of tyrosinase and INK protein. These activity of bavachinin makes it an potential candidate for the treatment of universal vitiligo to remove the remaining darken skin spots and providing an even skin tone**[75]**.

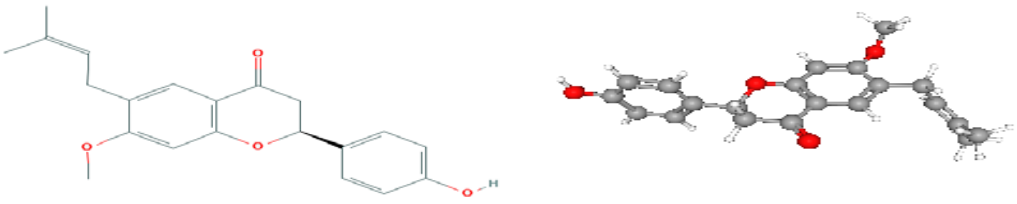
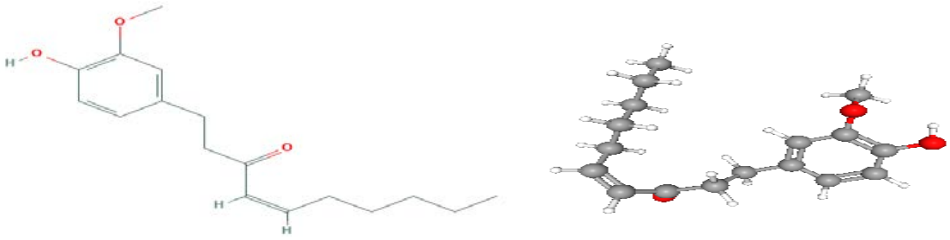


Figure 6: (a) 2D structure and (b) 3D structure of bavachinin.

Lingli Yang et.al, in their experiment they studied 6-shagaol (**Figure 7**), which is an major phytoconstituent of Zingiberofficinalewhich is able to attenuating oxidative stress stimulated ageing & neurotoxicity. They observed that 6-shagaol when used over vitiligo affected melanocytes it helps protecting melanocytes from H_2O_2 induced oxidative stress by activating NrF_2 pathway. These observations proves its efficacy in vitiligotreatment**[76]**.



(a) (b)

Figure 7: (a) 2D structure and (b) 3D structure of 6-shagaol.

K.H.Mou et.al, in their experiment in search of potential herbal candidate for vitiligo therapy they studied glycyrrhizin (**Figure 8),** which is an active component of Glycyrrhizaglabraand they observed in a clinical study that patients receiving combination therapy of UVB and glycyrrhizin showed 87.5% of total repigmentation. The mode of action involved in the effect of glycyrrhizin hypothesized to be its positive effects toward immunoglobuline E (TgE) i.e., immunomodulation**[77]**.

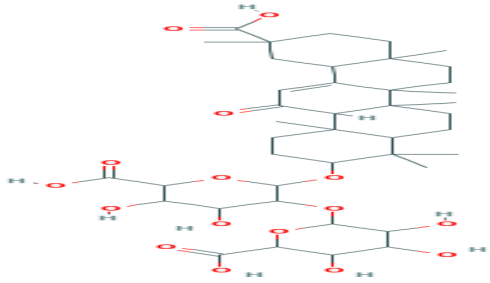
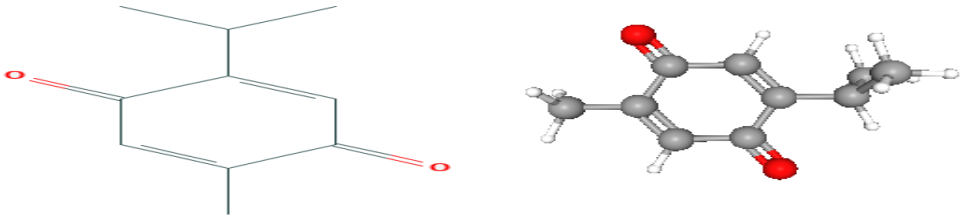


Figure 8: 2D structure of glycyrrhizin.

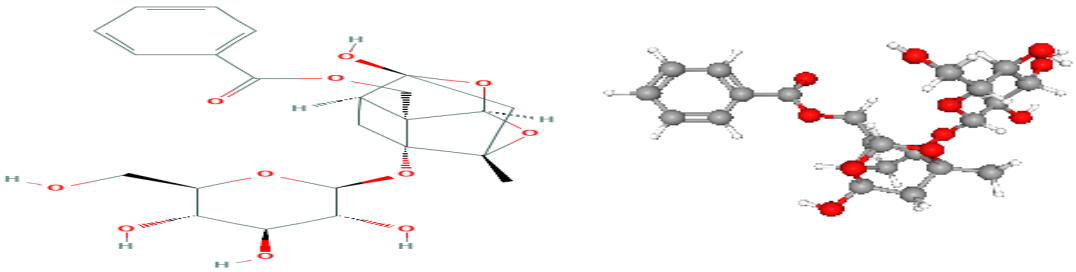
Sharique A Ali et.al, in their experiment on Nigella sativa they observed that thymoquinone (**Figure 9**) which is one of the major constituent of Nigella sativa showed promising results of skin darkening that is crucial for vitiligo therapy, it worked by stimulating pigment cells by enhancing cholinergic response that results production of melanin by melanocytes causing darkening of skin in lizards**[78]**.



(a) (b)

Figure 9: (a) 2D structure and (b) 3D structure of thymoquinone.

Jinping Yuan et.al, in their study over paeoniflorin (**Figure 10**) which is an monoterpene glycoside that is obtained from roots of PaeonialactifloraPall, observed that it can help in vitiligo treatment by preventing damage of melanocytes from oxidative stress by activating JNK/NrF_2/HO-1 pathway this activation of NrF_2 helps in expression of phase II antioxidant enzymes that further protects cells from oxidative stress**[79]**.



(a) (b)

Figure 10: (a) 2D structure and (b) 3D structure of paeoniflorin.

Mateo Becatti et.al, in their research they observed that reactive oxygen species production and mitochondrial damage in keratinocytes in vitiligo affected skin stimulate apoptosis through Smac/DIABLO & MAPK pathway, when the affected keratinocytes were treated with curcumin& capsaicin (**Figure 11**) it inhibits the intrinsic apoptotic pathway and helps in protecting progression of helps in protecting progression of the ailment**[80]**.

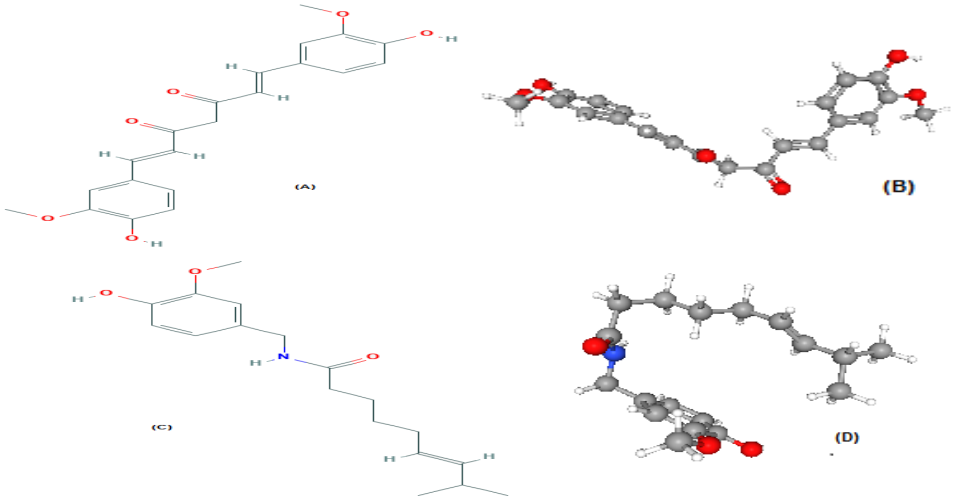
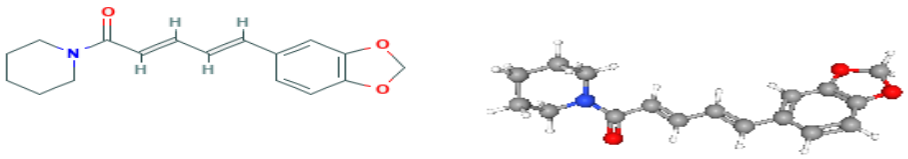


Figure 11: (A) & (B) curcumin 2D & 3D structure & (C) (D) Capsaicin 2D&3D structure.

Patrice Morliere et.al, in their clinical study over khellin (**Figure 12**) which is a major component of Ammivisnagaits potential in vitiligo treatment observed that the effects produced by khellin phototherapy is comparable to that produced by standard treatment of psoralen phototherapy i.e., upto 70% of skin surface of the involved skin showed complete repigmentation**[68]**.



(a) (b)

Figure 12: (a) 2D structure and (b) 3D structure of khellin.

Zhixiu Lin et.al, in their study on piperine (**Figure 13**) which is a major component of Piper nigrum, which possesses various therapeutic properties and are being used extensively in treatment of various ailments, one of the well-known properties is antioxidant property, they observed that piperine protects the melanocytes from oxidative stress and helps in the proliferation of these cells**[46]**

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(a) (b)

Figure 13: (a) 2D structure and (b) 3D structure of piperine.

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