Vitiligo Cured By Brosimum Gaudichaudii

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Abstract:-This review explores the severity of the vitiligodisease and a natural approach for its cure.Vitiligo is a chronic skin disorder characterized by the progressive loss of melanocytes, leading to depigmented patches on the skin. Affecting approximately 1-2% of the global population, vitiligo can significantly impact quality of life and psychosocial well-being. This review provides a comprehensive overview of vitiligo, including its classification, clinical symptoms, and underlying pathogenesis, which involves a complex interplay of innate and adaptive immunity, oxidative stress, and environmental factors. Additionally, we introduce Brosimum gaudichaudii, a tropical tree known for its medicinal properties, which typically grows to 20-30 meters in height and features broad, leathery leaves and small, cluster-like fruits. We detail its taxonomical classification, pharmacology, and chemical constituents. We explore the mechanisms of action of B. gaudichaudii and propose that its extracts may offer promising benefits in the treatment of vitiligo. By integrating current knowledge on the pathophysiology of vitiligo with the pharmacological properties of B. gaudichaudii, this review highlights the potential for this plant as a natural therapeutic agent in managing vitiligo.

Keywords: -Brosimum gaudichaudii, psoralens, vitiligo, leukoderma, bergapten, xantylene and innate immunity.

INTRODUCTION

The word vitiligo is originated from the *Latin* word vitium which means defect or blemish rather than vitellus, which means calf. Vtiligo is a common autoimmune disorder which was described 3500 years ago in Egyptian and Indian text. It affects 1% of the world's population. (Harris EJ, 2019).

Vitiligo affects a person's psychological and social well-being in a number of areas, including social relationships, mental health, and career prospects. A wide range of complicated emotional reactions, including anxiety, despair, and lowered self-confidence, can be triggered by the appearance of white spots on the skin (Salzer B 2009; Papadopoulos L 2011). These emotional reactions have the potential to seriously lower a person's general quality of life (Parsad D; 2003) affecting both the individual and those close to them. These are some complications which come with this disease; an accurate treatment is not available even at this time but the plant Brosimum gaudichaudii is used to treat the psoriasis and vitiligo due to the photosensitivity ability of its chemical constituents (psoralens). The plant Brosimum gaudichaudii is found in the Brazil. (Papadopoulos L 2011). These emotional reactions have the potential to seriously lower a person's general quality of life (Parsad D; 2003) affecting both the individual and those close to them. These are some complications which come with this disease; an accurate treatment is not available even at this time but the plant Brosimum gaudichaudii is used to treat the psoriasis and vitiligo due to the photosensitivity ability of its chemical constituents (psoralens). The plant Brosimum gaudichaudii is found in the Brazil.

Brosimum gaudichaudii is an important plant in the treatment of vitiligo, owing to its high quantities of linear furanocoumarins, particularly psoralen and bergapten, which are mostly found in the roots. These chemicals have been found to photosensitise by covalently connecting with DNA when activated by specific light wavelengths, making them useful in clinical studies for treating depigmentation disorders (Sumorek W *et.al.* 2020). Psoralen and bergapten have been used in combination with UV radiation to treat vitiligo, psoriasis, eczema, alopecia, and other systemic illnesses. While plant extraction is favored over costly chemical synthesis, which also generates damaging waste, overharvesting poses a considerable risk to the survival of Brosimum gaudichaudii (Nunes AR *et.al*, 2018; Ribeiro N *et. al*., 2020). The roots have the highest concentrations of these chemicals,

while the stem and leave have much smaller amounts (Melo DM 2004). Furthermore, only a small percentage of Brazil's vast biodiversity has been investigated for bioactive potential, highlighting the need for additional research (Ribeiro N *et. al.,* 2020). Therefore, sustainable harvesting procedures are vital to maintain the ongoing availability of this valued species while allowing for the therapeutic use of its bioactive chemicals.

DISEASE PROFILEOF VITILIGO:

Vitiligo is an acquired pigmentary disease with an unknown etiology that is clinically recognized by the appearance of white macules caused by melanocyte loss. The prevalence of the illness is approximately 1% in the United States and Europe, although it ranges from less than 0.1% to more than 8% worldwide. (Alikhan A, *et.al.*, (2011). Vitiligo is an autoimmune disorder with genetic, environmental, metabolic, and oxidative factors (Rodrigues M. *et. al.,* 2017). These factors are likely to interact in a variety of ways, resulting in the disease's numerous symptoms. Vitiligo is technically described as skin and hair follicle depigmentation that usually starts in areas of trauma (Koebner phenomenon) (Bergqvist C 2020).

Typical vitiligo lesions are milky white, non-scaly macules with noticeable edges. Vitiligo is an autoimmune skin disorder characterized by auto reactive CD8+ T lymphocytes that destroy melanocytes, the pigment-producing cells of the epidermis, resulting in depigmented areas. Patients with vitiligo require lifelong treatment to restore and maintain pigmentation. Clinical data indicated the role of immunologic memory in vitiligo, as quitting treatment typically resulted in disease recurrence at the site of previous lesions. CD8+ resident memory T cells (TRM) are a type of memory T cell found in most nonlymphoid tissues, such as the skin. They don't migrate. Recent findings reveal the occurrence of CD8+ TRM in lesional vitiligo patients' skin and suggest that they playan active part in disease maintenance. A recent worldwide consensus meeting recognized two basic kinds of vitiligo: segmental vitiligo and non-segmental vitiligo (also known as vitiligo). The most frequent form of this unpredictable condition is non-segmental vitiligo, which is distinguished by symmetrical, bilateral white patches. There are various clinical subtypes with a bilateral distribution, including universalis, acrofacial, and generalized sorts. Segmental vitiligo, on the other hand, is less common and typically presents as a unilateral distribution (Ezzedine k., 2015).

Fig No.01- Non-Segmental Vitiligo

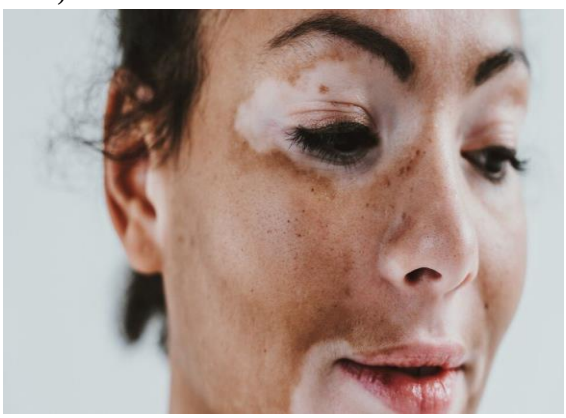

Fig No.02 – Segmental Vitiligo

Symptoms of vitiligo-

- White patches on skin
- Irregular shapes and sizes
- Hair in patches turns grey/white
- Symmetrical patches on both sides
- Sun-sensitive skin
- Itching or discomfort
- Patch growth over time
- Affects mucous membranes (e.g., lips)
- Emotional impact: Visible patches can lead to emotional distress, self-consciousness, and reduced self-esteem.

Pathogenesis:

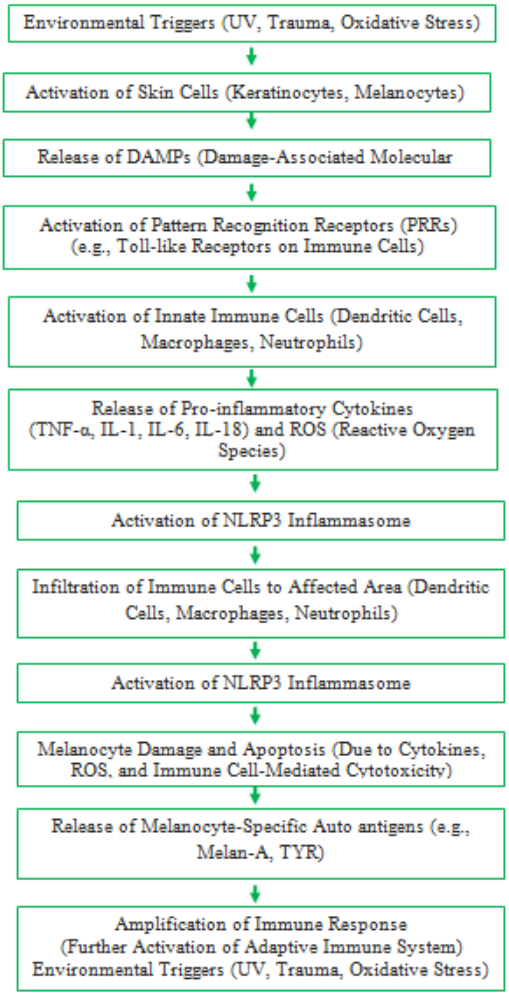

Fig No.03-Pathogenesis of Innate Immunity

BROSIMUM GAUDICHAUDII:

Brosimum gaudichaudii Trecul (BG) Moraceae, sometimes known as "mamacadela" and found in Brazilian cerrado shrubland, includes photosensitisers. The primary therapeutic application of BG is to treat vitiligo, a skin depigmentation disorder that affects 1-2% of the global population. Psoralen (PSO) and 5-methoxypsoralen (5-MOP) are widely used oral chemotherapeutics for vitiligo. EBGT root bark extract has considerable bioactive components.

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Mamacadela (Brosimum gaudichaudii) is a tree or shrub widely used in traditional medicine in the Cerrado region. The alcoholic extract of the roots is used to treat skin conditions including vitiligo. Its roots are infused to alleviate itching and bronchitis, as well as to cleanse the blood. (Pereira EB *et.al* 2006).

From Mamacadela roots, two furanocoumarins, bergapten and psoralen have been identified. Bergapten, a photosensitising agent that is linked to vitamins B1, B6, and A, is used to cure vitiligo. It is currently marketed as Viticromin and comes as topic solutions or cream (pomade). The impacted tissues' repigmentation is encouraged by the bergapten. Mamacadela has been heavily harvested from the wild due to commercial interest, which has led to significant pressure from anthropogenic exploitation (Pereira EB *et.al* 2006).

Psoralen (PSO) and 5-methoxypsoralen (5-MOP) are linear furocoumarins, generally referred to as psoralens, which are frequently used in oral photochemotherapy to treat vitiligo and psoriasis, among other skin conditions. Compared to other photosensitisers, 5-MOP often causes fewer acute adverse effects and a marginally higher tolerance in individuals. Because of the significant buildup of these psoralens in its roots, Brosimum gaudichaudiiTrécul (Moraceae) has garnered a lot of interest in this regard. (Machado RD *et.al* 2022*).*

The vast diversity of Brazilian flora and fauna is the result of several biomes found in the country, including the Amazon Forest, Caatinga, Atlantic Forest, Pantanal, Pampa, and Cerrado. As a result, Brazil boasts the highest biodiversity on Earth. The Biome Cerrado, which makes up over 22% of the country, is home to many native edible fruit species and is regarded as the second natural reserve of food and medicinal plants in the world. One could highlight the Brosimum gaudichaudii among the many Cerrado fruit species.


Fig No.04 And 05 –Leaves and Flowers Of Brosimum Gaudichaudii

Taxonomical classification:-

LEVEL	CLASSIFICATION
KINGDOM	Plantea
CLASS	Magnoliopsida
ORDER	Rosales
PHYLUM	Tracheophyta
FAMILY	Moraeceae
GENUS	Brosimum
SPECIES	Brosimum Gaudichaudii

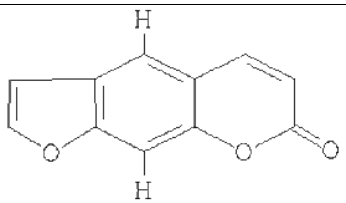
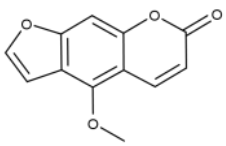
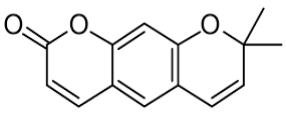
Table No 01: Taxonomical classification of Brosimum Gaudichaudii.(Haque E,2018)

Synonyms of brosimum gaudichaudii:

Alicastrum,Androstylanthus, Brosimopsis, Ferolia , Galactodendrum , Helianthostylis,, Lanessania , Piratinera, Trymatococcus. (Royal botanic garden kew 1847).

Chemical Constituents of Brosimum Gaudichaudii Root

Brosimum gaudichaudii root extract is commonly used in combination therapy to cure vitiligo. This extract contains bergapten and psoralens, which increase skin sensitivity to UV light and promote repigmentation when used with phototherapy. Combination Therapy When used with other therapies, such as topical corticosteroids or UV therapy, it can improve the overall efficacy of the protocol. These are the bioconstituents discovered in the roots of the brosimum plant that are used to cure vitiligo in a combination therapy; nevertheless, it has been noticed that relapse of the illness occurs when the treatment is stopped or discontinued. The tablets are made from the roots of plants that are found in a powdered form.

Sr. No	Chemicals responsible for the activity by roots	Structure	References
1.	Psorelens		Rai P. D (2010)
2.	Bergapten		Nielsen, B. E. (1970).
3.	Xantylethyne		Khan A.J. *et.al.*, (1985)

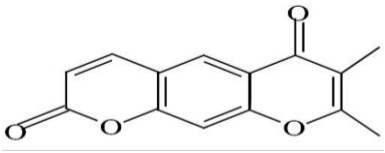
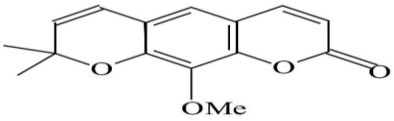
4.	Gaudichaudine		Anonymous.(2005)
5.	Luvgenthyne		Anonymous.(2005)

Table no 02: Chemical constituents of brosimum gaudichaudii roots.

The roots and lower stem of Brosimum gaudichianum (also known as Brosimum gaudichaudii) are recognized for their photosensitizing furocoumarins. Key compounds isolated from this plant include xanthyletine, bergapten, psoralen, luvangentine, and gaudichaudine, all of which exhibit photosensitizing capabilities. These compounds enhance the skin's sensitivity to UV light, making them valuable in phototherapy for treating conditions such as vitiligo. Additionally, similar synthetic furocoumarins are available in the pharmaceutical market, formulated into drugs designed to address vitiligo and other depigmentation disorders. The combination of these natural compounds with UVA light therapy (PUVA) can promote repigmentation in affected skin areas, highlighting their potential for innovative dermatological treatments. Viticromin is formulated with 80% root powder from Brosimum gaudichaudii in its tablets (400 mg in 500 mg of excipient), while the cream contains 20% powder (6 g in 30 g of excipient) and the solution has a 20% concentration (12 g of powder in 60 ml of excipient).These varying concentrations between the internal and external products account for potential losses during the pharmacokinetic processes, including absorption, distribution, metabolism, and excretion, before reaching the target area of the epidermis affected by vitiligo.

Despite its registration with the Brazilian Ministry of Health since 1968 and some clinical studies reporting up to 100% efficacy in repigmentation for certain cases (Azambuja R 1981; Anderson *et.al*., 1980; Auad, 1973), there is a lack of comprehensive research on the pre-clinical and clinical toxicity (acute, sub-acute, and chronic) and pharmacology for long-term treatment (5 to18months). Therefore, assessing the acute toxicity of Brosimum gaudichaudii in mice by determining the approximate lethal dose (ALD) and median lethal dose (LD50) is essential to meet regulatory requirements. (Cunha CL *et.al* (2008)

Mechanism of Action:-

The precise mechanism of pigment induction by PUVA in vitiligo is yet unknown. Psoralens promote melanogenesis. Photo conjugation of psoralens in melanocyte DNA causes mitosis, replication and proliferation of melanocytes, an increase in the quantity of melanosomes, and their subsequent transfer to keratinocytes (Sethi G and Sodhi A2004)

PUVA stimulates cyclic adenosine monophosphate (cAMP) activity, which leads to enhanced tyrosine production. PUVA also influences immunological processes and may produce a suppressor T cell population and release IL-10, which is critical for differentiation and activation of T regulatory cells that can suppress the auto-immune stimulation responsible for melanocyte death (Laing TJ 1995).

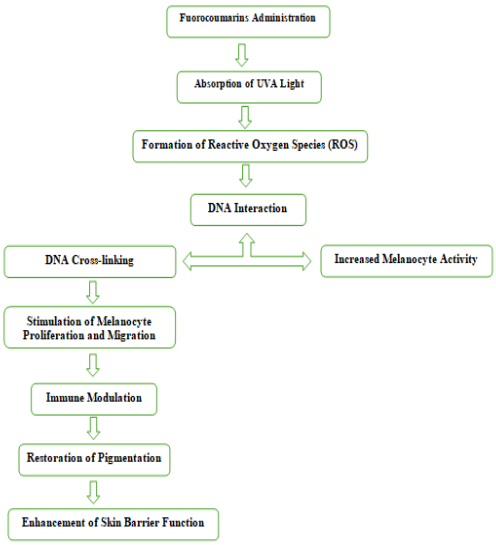


Fig no 06: Mechanism of action of fuorocoumarins.

Psoralens enter cells and intercalate between DNA bases. When exposed to UVA, psoralens absorb photons, get chemically activated, and covalently bond to DNA base pairs, generating crosslinks. DNA crosslinks exhibit antiproliferative, antiangiogenic, apoptotic, and immunosuppressive properties. The immunosuppressive consequences include cytokine and antigen presentation cell changes, decreased production of adhesion molecules, and lymphocyte death (Ceoviae R2007).

Pharmacology:-
After taking 8MOP orally, photosensitivity occurs one hour later, peaks at two hours, and then goes away at eight hours. (Martindale BG1989).

The physical properties of the preparation, concurrent meal consumption, and personal factors all affect the intestinal absorption rate of psoralens. Compared to micronized, crystalline formulations (like hard gelatin capsules), dissolved preparations (like soft gelatin capsules) are better absorbed and produce peak blood levels in a reasonably repeatable amount of time in all patients. Consuming food slows down and reduces psoralen absorption. Methoxsalen is transported throughout all organs in the circulation, where 75–80% of it is reversibly linked to serum albumin. Without UVA exposure, the binding is transient, the medication is quickly broken down in the liver, and the inactive metabolites are eliminated in the urine. Methoxsalen's metabolism is accelerated by drugs that activate cytochrome P-450 enzymes, which may also lessen the biologic action of PUVA (Ibbotson S.H *et. al.*, 2011)

Some biochemical markers may help explain the inter-patient variability in PUVA response; for instance, sensitivity to psoralen-UVA photochemotherapy is linked to the genotype of glutathione S-transferase. People who have a low maximal serum concentration and a high clearance typically exhibit less sensitivity to PUVA (Wolff F A, Thomas T V1986).

CONCLUSION

This review has explored vitiligo, focusing on its classification, symptoms, and the complex pathogenesis involving immune responses, oxidative stress, and environmental factors. Given the limitations of current treatment options, investigating alternative therapies is crucial.Brosimum gaudichaudii emerges as a potential therapeutic candidate due to its diverse chemical constituents and traditional medicinal uses. The presence of psoralens in the plant may offer insights into promoting repigmentation and enhancing treatment strategies for vitiligo.

While further research is needed to validate the efficacy and mechanisms of action of Brosimum gaudichaudii, this review emphasizes the importance of exploring plant-based therapies as complementary approaches. By integrating traditional knowledge with modern scientific research, we can enhance our understanding and management of vitiligo, ultimately improving outcomes for those affected by this condition.

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