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REVIEW ARTICLE

The Perspective of Unani Medicine in Understanding Melasma – A Review

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Abstract: Melasma, a prevalent hyperpigmentation skin disorder, poses significant challenges in dermatology clinics. Despite its global impact, conventional treatment options often entail potential side effects and limitations, necessitating the search for alternative therapeutic strategies.

This review aims to advance the understanding of melasma from the perspective of Unani medicine, an ancient healing system recognized by the World Health Organization. It seeks to explore potential therapeutic avenues within the Unani medical paradigm by synergizing ancient wisdom with contemporary perspectives.

The review delves into the Unani scholars' understanding of melasma referred to, as Kalaf, drawing from the wisdom of renowned scholars. Their insights into the multifactorial etiology of melasma, including pathogenesis, treatment approach, and recommended prescriptions, are discussed.

The descriptions of melasma by Unani scholars have documented the etiopathogenesis, risk factors, and management in detail and emphasize personalized interventions based on the pathological concepts of Unani medicine. Moreover, some of these interventions were also investigated in recent clinical trials and found to have comparable efficacy with standard treatment options.

This review fosters the understanding of the pathogenesis of melasma according to Unani concepts and a holistic approach to the management of melasma, drawing from the timeless legacy of the Unani system of medicine. This review may serve as a reference point for future research, enabling the planning of subsequent studies on this disease with a comprehensive understanding of the previous investigations conducted in this field.

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1. INTRODUCTION

Acquired hyperpigmentation skin disorders are frequently encountered in general dermatology clinics, with melasma being a prominent and challenging entity [1, 2]. In the Indian population, melasma is the most prevalent pigmentary condition, commonly observed in individuals aged between 30 and 40 years [1, 2]. Melasma is a notable cosmetic concern with a global impact [3]. The exact prevalence of melasma remains uncertain in South Asia, with estimates ranging from 0.25% to 4%. In India, melasma ranks as one of the most prevalent hyperpigmentary disorders, but precise prevalence data vary across regions [4]. In the United States alone, melasma affects between 5 to 6 million individuals, and its incidence is even higher worldwide [5]. Although predominantly observed in females, males constitute 10% of cases and exhibit similar clinicopathological features [1]. While melasma affects individuals of all races and ethnicities, it is more commonly found in those with darker skin tones (skin types 4 to 5), particularly among Hispanic, Asian, and African populations residing in regions with high UV radiation levels [4]. Studies report prevalence rates of 8.8% among Hispanic females in Texas. In Guerrero, Mexico, rural women exhibit a prevalence of 6%, while urban women show a prevalence of 4% [6]. Melasma exhibits a male-to-female ratio of 1:10, with the majority of cases occurring during the third or fourth decade of life, though lesions may also emerge after the age of 40 or 50 in 14% and 6% of cases, respectively [7].

Melasma manifests on the sun-exposed regions of the face [8], primarily affecting areas such as the forehead, cheeks, temples, and jaws, presenting as a nearly symmetrical aggregation of dark brown pigmented patches, often displaying distinct demarcations [9]. The forehead, cheeks, upper lip, nose, and chin are the most commonly affected regions [10]. Clinically, it manifests as brown, gray, or blue macules that coalesce to form irregular patches, lacking erythema or signs of

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irritation [8, 11]. Although it is often associated with women using oral contraceptives or during pregnancy [3, 12, 13], it can also manifest in both genders in the absence of hormonal influence [3, 12, 14]. Previous beliefs attributed hyperpigmentation solely to epidermal melanin, but current research indicates that an increased number of melanocytes may contribute to the epidermal hyperpigmentation observed in melasma [15].

Although melasma can occur in individuals of any skin type, it exhibits a notably higher prevalence in those with darker skin phototypes (Fitzpatrick Skin Phototypes IV to VI) who are exposed to significant levels of ultraviolet light [1, 8, 16]. Furthermore, a distinctive hallmark of melasma lies in the presence of blotchy areas of normal skin amidst the pigmented patches [17].

Morphologically, melasma can be classified into three patterns: centrofacial, malar, or mandibular [17]. Centrofacial melasma stands as the most prevailing type, affecting the brow, nose, upper lip, chin, and medial cheeks [18]. Histologically, melasma can be classified into different types based on the location of melanin deposition. The most common type is the epidermal type, characterized by an increase in melanin content within the epidermis, with only a few melanocytes observed in the upper dermis. Conversely, the dermal type exhibits the presence of numerous melanophages distributed throughout the entire dermis. Another type is the mixed type, where both epidermal and dermal regions display increased melanin, and a significant number of melanophages are scattered within the dermis. Additionally, an indeterminate type is observed in individuals with Fitzpatrick skin types V-VI, which are skin types that very rarely or never burn [17].

Melasma is characterized by an upregulation of dermal and epidermal melanin production and retention [19]. Keratinocytes in melasma-affected skin exhibit overexpression of vascular endothelial growth factor, which may influence melanocyte behavior [20]. Solar elastosis, indicative of cumulative sun exposure, is significantly associated with the pathogenesis of melasma. Histological examination reveals notable pathological changes in melasma-affected skin, including photodamage, vascularization, inflammation, and heightened melanogenic activity, distinguishing it from non-affected perilesional skin [21, 22].

Melasma can be triggered by the activation of estrogen receptors on melanocytes, which stimulates these cells to produce excess melanin. The condition tends to run in families and is more commonly observed in individuals of Asian and Hispanic heritage, indicating a genetic influence. Additionally, melasma has been associated with the use of photosensitizing and anticonvulsant medications, minor ovarian or thyroid abnormalities, and certain cosmetic products [23].

Melasma management is complex and needs a protracted treatment regimen. Conventionally, numerous topical therapy options are available including topical hypopigmenting medicines such as hydroquinone, kojic acid, and azelaic acid [24], with hydroquinone being the most frequently prescribed medication[4]. It works by preventing the conversion of DOPA to melanin *via* the tyrosinase enzyme [25]. Hydroquinone monotherapy and triple combination cream (hydroquinone, tretinoin, and corticosteroid) are the most successful and well-established treatment options for melasma, whilst chemical peels, laser and light-based therapies are comparable to topical but have a greater risk of unpleasant effects [26].

Conventional treatment options for melasma can pose adverse reactions. Hydroquinone, a commonly used agent, may lead to dose and time-related effects, including erythema, stinging, and paradoxical postinflammatory hypermelanosis. Higher concentrations of hydroquinone (>2%) can cause "confetti-like" depigmentation. Long-term use may lead to ochronosis [27]. Topical corticosteroids, used to reduce irritation, may cause skin lightening and, with prolonged use, lead to skin atrophy and other issues [28].

Given these potential side effects and limitations associated with conventional treatments, the exploration and development of alternative therapeutic options have become increasingly crucial. Researchers and clinicians are actively seeking safer and more effective approaches to address melasma, aiming to provide patients with improved outcomes and minimized risks of adverse reactions. Consequently, in this pursuit, the traditional system of medicine may play a pivotal role. By delving into the knowledge and wisdom of ancient healing practices, such as Unani medicine, novel therapeutic approaches and potential remedies for melasma could be unearthed.

Traditional systems of medicine encompass diverse methodologies for addressing various diseases, each characterized by its own nomenclature and classification [29-31]. Globally, multiple traditional systems of medicine have garnered recognition from the World Health Organization (WHO) [32]. Unani, an ancient system of medicine that originated in Central Asia, evolved from the teachings and principles of the renowned Greek physician Hippocrates (460-370 BC). Subsequently, it underwent elaboration and refinement through the contributions of Roman physician Jālinūs (Galen, 129-210 CE), Arab and Persian physicians Zakariyya al-Rāzī (Rhazes, 850-925 CE), Shaykh al-Rayīs Abdullah Ibn Sīnā (Avicenna, 980-1037 CE), Abu'l-Qāsim al-Zahrawi (Abulcasis, 936-1036 CE), and Ibn Nafīs (1213-1288 CE) [33,34]. In India, Unani experienced sustainable growth, witnessing advancements in practice, education, and research [34-36]. The Unani system of medicine revolves around seven key principles: *Arkān* (elements), *Mizāj* (temperament), *Akhlāt* (humours), *A'za* (organ), *Arwāh* (pneuma), *Quwwā* (faculties), and *Af'āl* (functions), collectively referred to as *Umūr-i Tabiyya*. Disruptions or deficiencies in these components pose significant threats to the maintenance of health and give rise to diseases [37]. Built on scientific and holistic concepts of health and healing, the Unani system's fundamental principles, diagnostic approaches, and treatment modalities derive their foundation from these core tenets. The system takes into account the whole individual, eschewing a reductionist approach to health and disease [34]. The demand for Unani medicine is steadily increasing owing to its proven efficacy and minimal adverse effects [35,38,39]. This venerable healing tradition serves as a testament to the enduring value of ancient wisdom and its timeless relevance in the pursuit of optimal health and well-being.

Melasma has received considerable attention in the traditional literature of the Unani system of medicine. Renowned physicians and scholars have extensively explored this condition under the designation of '*Kalaf*' in their scholarly works. Within the Unani framework, these esteemed scholars have provided comprehensive insights into the multifactorial nature of melasma. Etiological factors, encompassing humoral imbalances, environmental influences, and lifestyle choices, are intricately analyzed which underlies the pathophysiology of melasma. Notably, the Unani approach to melasma management emphasizes personalized interventions based on individual temperaments and humoral imbalances. Therapeutic modalities encompass a diverse range of natural remedies, including herbal formulations, dietary modifications, and lifestyle adjustments, all aimed at restoring equilibrium and promoting rejuvenation.

In this current review, we delve into the vast reservoirs of knowledge offered by these venerable Unani scholars. Our objective is to advance our comprehension of melasma while exploring potential therapeutic avenues within the Unani medical paradigm. By synergizing ancient wisdom with contemporary perspectives, we aspire to unveil novel insights into melasma and foster a holistic approach to its management, drawing from the timeless legacy of the Unani system of medicine.

2. METHODOLOGY

The researchers systematically explored both historical and modern scientific literature to identify references to melasma, focusing specifically on Unani medicine. This comprehensive examination aimed to gather and interpret information pertinent to the historical context, etiology, pathophysiology, clinical manifestations, diagnostic methods, and therapeutic approaches related to melasma within the Unani system of medicine. The scholarly contributions of classical Unani figures such as Avicenna, Zakariya Razi, Ali Ibn Abbas Majusi, AH Quamri, Rabban Tabri, Ahmed bin Muhammad Tabri, Azam Khan, Hafiz Jaleel, Akbar Arzani, and Ajmal Khan were meticulously scrutinized and analyzed. Additionally, a targeted online search was conducted across electronic databases, including PubMed, ScienceDirect, and Google Scholar, to uncover recent clinical trials involving Unani medicinal compounds or formulations. The search also extended to the clinical trial registry of India to identify ongoing research in this area. Boolean logic operators 'AND', 'OR', and 'NOT' were employed strategically in the search process. The terminology and transliterations specific to Unani medicine were referenced from the latest standardized lexicon for the field.

3. RESULTS

3.1. Background Timeline of Melasma in Unani Medicine

The historical evolution of the understanding and description of melasma within the Unani system of medicine spans over millennia, with eminent scholars and physicians contributing their valuable insights.

The earliest mention of melasma is attributed to the renowned ancient Greek physician Hippocrates (470-360 BC), who described hyperpigmented facial sores exacerbated by heat and sunlight [40]. During the medieval era, Rabban Tabri (770-850 AD) presented the earliest comprehensive description of melasma in his book *Firdausul Hikmat*, attributing its origin to morbid stomach vapors [41]. Hakim Hafiz Jalil, in his book *Tazkira-i Jalil*, shared Tabri's prescription for melasma treatment using a combination of natural ingredients [42]. Abul Hasan Ahmad bin Mohammad Tabri (780-850 AD), in his seminal work *Mu'alajat-i Buqratiyya* stated that Kalaf arises from blood extravasation, wherein the crimson fluid escapes the confines of small capillaries and lodges itself between the skin and muscles without undergoing dissolution [43].

Thabit bin Qurrah (836-901 AD), a meticulous documenter of *Sawdāwī* (melancholic) diseases, expounded on Kalaf's etiology, attributing its development to morbid blood and excessive stomach vapor. Furthermore, he observed its occurrence during pregnancy, illuminating the intricate relationship between hormonal changes and the manifestation of melasma [44]. Zakariya Razi (850-823 AD), celebrated for his influential treatise Al-Hawi, contributed valuable insights into Kalaf. He identified its genesis because of ruptured, contused, or congested facial veins, leading to subcutaneous bleeding. The accumulation of blood beneath the skin imparts the characteristic darkening of the affected areas [44]. Quamri (9th Century AD) shared insights in Ghina Muna that Kalaf exhibits a higher prevalence in postpartum women. He posited that this may be linked to the cessation of puerperal blood, with the remnants of morbid material potentially contributing to the appearance of melasma [45].

Majūsī (936-1030 AD) endearingly referred to *Kalaf* as *Jhayyn* and considered the evacuation of black bile (*Tanqiya-i Sawdā*) as a plausible treatment strategy [11, 46]. Ibn Sina (980-1073 AD), a towering figure in the history of medicine, expounded upon causative factors of *Kalaf* in his renowned work *Al-Qanoon fi'l-Tibb*. He attributed its occurrence to the accumulation of morbid blood and damage to the capillaries leading to the vascularization of the upper layer of the skin [47] and suggested remedies to address this condition such as venesection [48].

Ibn Zuhar (11th Century AD), a distinguished Unani scholar and author of *Kitāb al-Taysīr*, elucidated that the convergence of menstruation blood with regular blood circulating throughout the body may lead to the manifestation of *Kalaf* [49].

According to Ibn Hubal Baghdadi (1122-1213 AD), *Kalaf* refers to the presence of black and pustule-like spots on the skin. To treat this condition, evacuation of black bile is deemed necessary, while in certain cases, incision is recommended [50]. Ismail Jurjani (12th Century AD) advocated the use of *Tanqiya* (evacuation) through *Joshanda Halīla* and *Aftīmūn* (decoction of *Terminalia chebula* and *Cuscuta reflexa*), which proves beneficial in managing Kalaf, as documented in his book Zakheera Khawarizm Shahi [51].

Najeebuddin Samarqandi (13th Century AD), a prominent Unani scholar, described *Kalaf* as arising due to *Sawda-i Muhtaraq* (burnt black bile), resulting in bluish-black or reddish marks on the face. Its management involves the evacuation of *Sawda-i Muhtaraq* through *Adviya-i Mushila* (purgative drugs), exemplified by *Ma' al-Jubn* (whey), and subsequent topical application of *Jāli* (detergent) and *Muhallil Advia* (anti-inflammatory agents) such as *Bādām Talkh* (*Prunus amygdalus* var *amara* DC. Focke) and *Būra Armanī* (silicates of alumina) [52].

Akbar Arzani (1772 AD) depicted *Kalaf* as a skin condition where the complexion turns blackish and bluish, often accompanied by red patches on the face. He highlighted the beneficial effects of *Rewand Chīnī* (*Rheum australe* D. Don) in combination with honey for the treatment of *Kalaf* [53].

Azam Khan (1813-1902 AD) observed that *Kalaf* predominantly affects pregnant women, possibly due to spleen weakening and *Ihtibās-i Ṭams* (amenorrhea) in women [54]. Hakim Ajmal Khan (1868-1927) described *Kalaf* or *Jhayyn* as the appearance of little brown and blackish spots on the face and dorsum of the hand, likely resulting from direct exposure to sunshine and heat [55].

Kabiruddin (20th Century) emphasized the necessity of tailored treatments for *Kalaf*, suggesting treatment for cases linked to menstrual blood cessation, while recognizing the likelihood of spontaneous resolution for pregnancy-related instances [56].

3.2. Etymology

The term '*melasma*' finds its roots in the Greek word *'melas,'* meaning black, while *'chloasma'* originates from the Greek word *'khloazein,'* signifying green [57]. Additionally, melasma is commonly referred to by various names in different contexts, such as '*mask of pregnancy*' [1, 5, 7, 12, 17, 58, 59], *'mask-like pigmentation'* [1, 7], *'chloasma'* [1, 12, 17, 25, 59-63], *'chloasma faciei'* [4], *'swarthy spots'* [64], *'Kalaf'* and '*Jhāyyn*' [48].

3.3. Synthesized Description of Melasma in Unani Medicine

3.3.1. Definition of Kalaf

Kalaf, as expounded in the esteemed Unani medical literature, is characterized by the presence of bluish, black, or red patches on the facial skin. It arises due to the accumulation of scorched blood beneath the dermis and is predominantly observed on the cheeks, forehead, and upper lips [65]. Occasional manifestations of bluish-black or reddish marks, particularly on facial areas, add further intrigue [52, 53]. Eminent scholars such as Ibn Sina and Ibn Hubal Baghdadi attribute the etiology of *Kalaf* to the sequestration of blood resulting from capillary rupture or damage. The descriptive terminology of this condition varies based on the hue of the trapped blood, with '*Namash*' denoting reddish, '*Barsh*' signifying blackish, and '*Kalaf*' describing blood akin to coagulated consistency [11, 42, 48]. Kalaf exhibits a distinct form of facial discoloration, often arranged in a circular pattern without any noticeable elevation [66]. Aligning with the observations of Najeebuddin Samarqandi, Kalaf is characterized by captivating blackish pigmentation and the emergence of alluring bluish-black or reddish markings on the facial surface [52].

3.3.2. Risk Factors of Kalaf

The venerable Unani scholars have identified several primary risk factors for Kalaf, which include exposure to sunlight, consumption of a high-fat, uncooked, and unhealthy diet, dyspepsia, alcohol intake, blood infection, amenorrhea, and pregnancy [41, 52, 55]. Moreover, certain foods such as peas, grape juice, rice, milk almond porridge, and lamb meat, along with *Sawdā*' producing Advia (medicines) or Aghziya (foods), were linked to this condition [67].

3.3.3. Etiology of Kalaf

The etiology of the disease, as extensively described by ancient Unani scholars, encompasses a diverse array of factors contributing to its manifestation. Among these factors is *Sawdāwī Khūn* (melancholic blood) [43]. Additionally, vapors arising from the stomach and affecting the facial region are implicated in the development of the condition [41, 68]. The presence of *Dam Muhataraq* (burnt sanguineous humor) has been linked to the onset of the disease [11]. Morbid blood has also been identified as a contributing factor [48, 68]. Furthermore, the presence of *Ghalīz wa Fāsid Mawād*, referring to viscid and morbid matter, plays a role in etiopathogenesis [50]. The cessation of menstrual blood has been recognized as a relevant factor [42]. Additionally, *Sawdā-i Muhtaraq*, or burnt black bile, is associated with the condition [52, 53]. Prolonged exposure to sunlight and heat has been implicated as a potential trigger. Unhygienic lifestyle practices may also contribute to the disease occurrence [55]. Weakness of the spleen and *Ihtibās-i Tams*, indicating retention of menses, has been identified as further relevant factor [54]. Finally, facial skin abrasion has been included among the etiological elements [69]. The multifactorial nature of these etiological factors underscores the complex pathogenesis of melasma in the context of Unani medicine.

3.3.4. Pathogenesis of Kalaf

The pathogenesis of Kalaf (melasma), as elucidated by Unani scholars, revolves around the ascent of viscid melancholic vapors or fumes toward the facial skin and pores [54]. This process is further influenced by sun exposure and heat, leading to revascularization in the upper layers of the skin and subsequent blood sequestration and the formation of *Sawdā' Damawī Muhtaraq* (burnt melancholic blood) due to capillary damage [47]. The increased vascularization contributes to the heightened activity of epidermal and dermal cells, particularly an overexpression of melanocytes, resulting in elevated melanin synthesis and the development of melasma, as described in conventional medicine [19, 47].

Several factors contribute to the emergence of viscid melancholic vapors. Firstly, the condition may arise during pregnancy or the postpartum period, leading to *Ihtibās-i Tams* (retention of menses) or cessation of purpureal blood. This cessation can cause the accumulation of blood and waste material, along with the formation and derangement of *Sawdā*, ultimately leading to viscid melancholic vapors [54, 67]. Secondly, the consumption of *Sawdāwī* foods or the presence of *Sawdāwī Fuzlāt* (melancholic wastes) in the body can generate contaminated stomach gases, leading to the formation of *Bukhārāt-i Sokhta* (burned vapors) and subsequent viscid melancholic vapors [46]. Lastly, individuals affected by quartan fever or other *Sawdāwī* diseases may experience spleen weakening. The spleen plays a vital role in regulating *Sawdā*, and its impairment to separate black bile from blood or impaired absorption of Sawdā can result in an excess of *Sawdāwī Fuzlāt* in the body, ultimately leading to the development of viscid melancholic humor [54]. Fig. **1** depicts the schematic representation of the pathogenesis of melasma according to Unani scholars' insight.

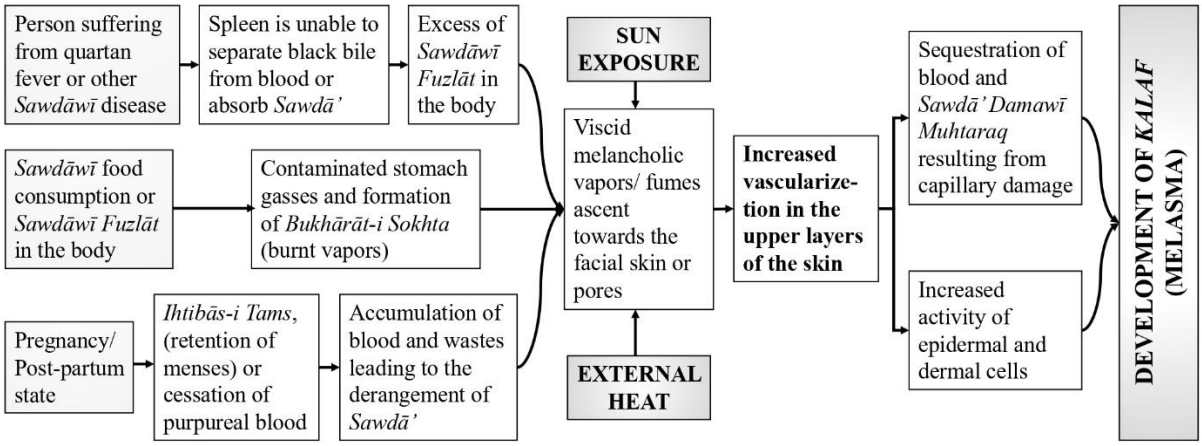

Fig. (1). Schematic representation of the pathogenesis of melasma according to unani scholars.

3.3.5. Classification of Kalaf

Jalinūs described Kalaf as a unified entity without any subtypes; however, Hakim Hafiz Jalil later presented a more comprehensive perspective, distinguishing between congenital and acquired Kalaf. The congenital type is known to be particularly challenging to treat, while the acquired form can be treated or may resolve naturally after the puerperium period [70]. Moreover, a recent classification proposed by a scholar introduced a categorization based on etiological factors, giving rise to four distinct subtypes of Kalaf, namely *Kalaf-i Rahimi, Kalaf-i Kabidī, Kalaf-i Zarabī, and Kalaf-i Hurrī*. *Kalaf-i Rahimī* is associated with pregnancy, the use of oral contraceptive pills (OCPs), and humoral imbalances. *Kalaf-i Kabidī* is linked to liver disorders and may be related to other gastrointestinal diseases. *Kalaf-i Zarabī* is characterized by abrasion or injury to the facial skin as a causative factor. Lastly, *Kalaf-i Hurrī* is influenced by excessive heat exposure, particularly due to prolonged sunlight exposure [70].

3.3.6. Clinical features of Kalaf:

The clinical features of Kalaf include the presence of blackish or papular spots on the facial region [50], as well as the regal hues of purple, blackish, or reddish spots on the face [52]. Additionally, they describe the subtle nuances of color, with purple or reddish spots gently gracing the facial canvas [53]. Furthermore, the clinical picture encompasses brownish or blackish spots on the face and an associated sensation of itching. Moreover, the Unani scholars have keenly observed that the condition may be accompanied by a sense of depression, particularly in women [55].

3.3.7. Diagnostic approach

Kalaf (melasma) is diagnosed clinically, following the insights of Unani scholars. A meticulous examination of the characteristic skin manifestations and pigmented patches on sun-exposed facial areas is conducted to confirm the diagnosis. Each patient evaluation involves a comprehensive assessment of potential risk factors and triggers associated with melisma [71].

3.3.8. Differential diagnoses

In the Unani system of medicine, differentiation from Kalaf is essential for several forms of hyperpigmentation cases, and comprehending these distinct conditions is crucial for precise evaluation and management. The Unani scholars have provided detailed descriptions of the clinical features of these differential diagnoses, facilitating their identification and differentiation:

Bahaq Aswad: This condition involves the darkening of the skin, particularly affecting regions such as the chest, abdomen, back, and forelimbs. It arises from the preponderance of *Ṣafrā' Muharraq* (burnt yellow bile) within the body [65]. The skin affected by *Bahaq Aswad* may exhibit a rough texture and tiny scales, providing vital clues for distinguishing it from Kalaf [52, 55]. A potential correspondence has been suggested between *Bahaq Aswad* and pityriasis nigra [65].

Baraṣ Aswad: In the case of *Baraṣ Aswad*, the skin presents with darkened patches accompanied by scaling, resulting in a roughened surface. The accumulation of black bile beneath the skin contributes to its manifestation, resembling certain aspects of Kalaf [65]. Some Unani scholars have considered *Baraṣ Aswad* and *Qūbā* (tinea) to be synonymous entities, underlining the importance of precise differentiation [52, 53].

Barash: Characterized by the presence of multiple small-sized black spots, Barash often displays reddish or bluish hues on the facial skin [52, 53]. The underlying cause is attributed to the accumulation of *Sawdā'* (black bile) beneath the skin. A potential similarity between Barash and freckle lentigo/ephelis/ephelides has been suggested, emphasizing the need for careful observation during the diagnostic process [65].

Namash: It presents as reddish, blackish, or violet patches, occasionally taking on a circular configuration, and is frequently present from birth. Its distinctive congenital nature sets it apart from Kalaf. Scholars have proposed Naevus as a possible counterpart to *Namash*, warranting thorough clinical evaluation [65].

Khīlān/Til: The presence of circular black patches, slightly elevated from the skin surface, characterizes *Khīlān* or *Til*. The abundance of *Sawdā' Muhtaraq* (burnt black bile) contributes to its formation. This condition shares some features with moles, necessitating meticulous examination and differentiation [52].

3.3.9. Management of Kalaf

3.3.9.1. Approach

Unani academics have meticulously documented the *Usūl-i 'Ilaj wa 'Ilaj* (principles and methods of its treatment) in their revered texts. In the management of Kalaf, Unani physicians employ a multifaceted approach that encompasses risk factor modifications, *'Ilāj b'il Ghiza wa Tadbīr* (diet and regimen therapy), *'Ilāj bi'l Dawa* (pharmacotherapy), and '*Ilāj-i Nafsānī* (psychotherapy) [54,71]. Furthermore, Unani scholars have emphasized the importance of prompt treatment, as chronic Kalaf can be challenging to manage [48].

3.3.9.1.1. Risk factors modifications

To modify risk factors, it is essential to avoid excessive sun exposure, address stomach disorders, and address menstruation abnormalities in women, as these factors can contribute to the development or exacerbation of Kalaf [54].

3.3.9.1.2 'Ilāj bi'l Dawa

Pharmacotherapy in Unani medicine involves the use of herbal medicines, minerals, and animal-derived substances to address the underlying imbalance and restore equilibrium within the body. Unani physicians have recommended *Tanqiya-i Sawdā'* (evacuation of black bile) as the initial therapeutic approach for managing Kalaf, employing purgative (*Munzij*) and laxative (*Mushil*) interventions specifically targeting *Sawda'* (black bile) [46]. This is followed by *Taqwiyat-i Mi'da*, the administration of *Muqawwi-i Mi'da* (stomach tonic) medicines [53][72], and *Tasfiya-i Jild*, which involves the application of *Jālī Advia* (detergent drugs) to cleanse the skin [71]. Furthermore, *Qawī Muhallilāt* (strong purgatives) are employed in cases of chronic Kalaf, while *Dāfi'-i Muḥallilāt* (anti-inflammatory) are utilized during the early stages of the condition. The choice of medication may vary based on the disease stage, and in the initial stages of resolution, medications with astringent properties are recommended. However, it is crucial to exercise prudence when using these medications for an extended duration, and they may be employed in combination with resolvent drugs to achieve the desired therapeutic outcomes for Kalaf management [48].

The principle of *Tanqiya-i Mawād* (expulsion of morbid matter) serves as the foundational concept in Unani therapy for the treatment of chronic diseases, including Kalaf. This therapeutic approach is characterized by a series of systematic procedures aimed at the removal of pathogenic humours from the body. The process commences with *Istifragh* (evacuation), a methodological elimination of diseased humours [73]. Preceding *Istifragh*, the method of *Nuzj* (concoction) is employed, involving the administration of *Munzij Advia* (concoctive drugs) corresponding to the specific humour in question. *Nuzj* represents a specialized procedure that alters the consistency of the diseased humour, facilitating its subsequent removal from the body. Upon the identification of the indicators of *Nuzj* in relation to the accumulated humour, the actual procedure of Istifragh is executed through an array of methods. These include *Ishāl* (purgation), *Faṣd* (venesection), *Hijāma* (cupping), *Irsāl-i 'Alaq* (leeching), *Tanfīth* (expectoration), *Qay'* (emesis), *Huqna* (enema), *Ta'rīq* (diaphoresis), *Idrār* (diuresis), *Hammām* (Turkish bath), *Riyāzat* (exercise), *Dalk* (massage), among others. Of these, *Ishāl* (purgation) is the most frequently utilized modality in the *Istifragh* treatment paradigm [54]. Following the process of purgation, Unani scholars have recommended the administration of medicines possessing a cold temperament, preferably with tonic properties. This recommendation arises from the observation that purgation can induce excessive dryness and heat within the gastrointestinal tract, leading to an abnormal increase in hot temperament. In some instances, this may result in intestinal erosions and subsequent bleeding. To mitigate these undesirable effects, a regimen known as *Tabrīd* (cold regimen) must be systematically prescribed. This approach serves to counterbalance the unwanted adverse effects of purgatives and aids in restoring the normalcy of temperament within the body [74].

3.3.9.1.3. 'Ilāj bi'l Tadbīr

Regimen therapy holds significant importance in the Unani treatment of Kalaf. Unani physicians prescribe venesection (*Faṣd*) to facilitate *Tanqiya-i Raddi Akhlāt* (evacuation of morbid humors), which can be performed as an initial step before commencing pharmacotherapy [53][72]. Additionally, cupping therapy, as recommended by Ibn Sina, is advocated as a preparatory measure before cleansing the lesion of Kalaf [48]. Furthermore, some Unani scholars suggest the use of *Irsāl-i 'Alaq* (leeching) as an additional therapeutic option for managing Kalaf [54].

3.3.9.1.4 'Ilāj b'il Ghiza

Diet therapy focuses on maintaining the balance of humors within the body, as an imbalance of *Sawdā'* (black bile) is considered the root cause of Kalaf. Special attention is given to the choice of foods, their preparation, and the timing of meals to promote overall health and harmony.

3.3.9.1.5 'Ilāj-i Nafsānī

It forms an integral part of Unani treatment, acknowledging the strong connection between the mind and body. Emotional and psychological factors are taken into consideration as they may influence the course of the disease. Stress management techniques, counseling, and relaxation practices are often incorporated to promote emotional well-being and enhance the overall healing process [71].

3.3.9.1.6. 'Ilāj bi'l Yad:

If Kalaf does not respond satisfactorily to the above-mentioned therapeutic options, an incision may be necessary for treatment [45,50].

3.3.9.2. Treatment Options

3.3.9.2.1. First line of treatment

The recommended first line of treatment for *Kalaf* is ***Tanqiya Sawdā'*** **(evacuation of black bile)** according to Ibn Hubal Baghdadi but Ibn Sina suggested ***Faṣd*** **(venesection)** as the first line of treatment.

1. Tanqiya Sawdā'

According to the renowned scholar Ibn Hubal Baghdadi, the therapeutic regimen for *Tanqiya Sawdā'* should commence with the administration of specific substances such as *Mā' al-Jubn* (Whey), *Halīla* (Terminalia chebula Retz.), *Af-*

tīmūn (*Cuscuta epithymum* L.), and *Gāozabāṉ* (*Borago officinalis* L.) [50]. Additionally, other Unani pharmacological agents can be systematically employed in *Nuzj*, *Ishāl*, and *Tabrīd*, as delineated below [73]:

a) Munzijāt-i Sawdā' drugs options:

a) *Bādranjboya* [*Melissa axillaris* (Benth.) Bakh. f.]

b) *Bisfā'ij* (*Polypodium vulgare* L.),

c) *Halīla Siyāh* (*Terminalia chebula* Retz.),

d) *Usṭūkhudūs* (*Lavendula stoechas* L.),

e) *Aftīmūn* (*Cuscuta reflexa* L.),

f) *Mā al-Jubn* (whey), *etc*.[73].

b) Mushilāt-i Sawdā' drugs options:

a) *Maghz Amaltās* (*Cassia fistula* L.)

b) *Barg-i- Sanā* (*Senna alexandrina* Mill.),

c) *Turbud* [*Operculina turpethum* (L.) Silva Manso],

d) *Ghārīqūn* (*Agaricus alba* L.), *etc*. [73].

c) Tabrīd Drugs Options

a) *Luāb-i Resha Khatmi* (*Althaea officinalis* L.)

b) *Shira Bādiyan* (*Foeniculum vulgare* Mill.),

c) *Shīra Luāb-i Behīdāna* (*Plantago ovata* Forssk.)

d) *Shīra Unnāb* (*Zizyphus sativa* Gaertn.),

e) *Tukhme Kasni* (*Cichorium intybus* L),

f) '*Arq-i Shāhtara* (*Fumaria parviflora* Lam), *etc* [73].

2. Faṣd **(Venesection)**

- *Ibn Sīnā* recommended *Faṣd-i Arnaba* (venesection of veins around the nose) [48].
- A H Quamri recommended *Faṣd-i Qīfāl* (venesection of the cephalic vein) [45].
- Azam Khan suggested *Faṣd-i Bāsalīq* (venesection of the basilic vein) and *Faṣd-i Usailum* (venesection of the salvatella vein) [54].
- According to Razi, Kalaf, induced by morbid blood, is optimally treated with cephalic vein venesection and oral administration of *Matbūkh Aftimūn* [75].

Furthermore, Unani scholars have delineated the therapeutic approaches into two distinct categories: *systemic and topical treatments.*

3.3.9.2.2. Systemic treatment options for Kalaf

Quamri's treatment approach: Hakim A.H. Quamri recommends the initial administration of *Joshānda Aftimūn* (*Cuscuta epithymum* L. concoction). In cases where *Kalaf* exhibits a more blackish hue, the same treatment sequence should be applied, with the subsequent administration of *Mā al-Jubn* [52]

Ibn Hubal Baghdadi's treatment approach: According to Baghdadi, *Istifrāgh* (evacuation) should be executed after the hot fomentation of the facial region [50].

Ibn Sina's treatment approach: Ibn Sina also suggests the use of *Joshanda Iklīl-al-Malik* (concoction of *Astragalus homosus* L.) in combination with *Āb-i Hulba* (*Trigonella foenum-graecum* herb decanted water) for the treatment of Kalaf [48].

Azam Khan's treatment approach: If Kalaf presents with greenish and yellowish coloration due to the accumulation of *Sawdā* in the stomach or stomach inefficiency, *Tanqiya-i Badan* (evacuation of morbid matter from the body) and *Taqwiyat-i Mi'da* (toning up of the stomach) should be performed [54].

3.3.9.2.3. Topical treatment options for Kalaf

Treatment for Kalaf with macules: If Kalaf is accompanied by macules, a therapeutic paste should be prepared with 7g *Gil-i Armani* (silicates of alumina), 3.5g *Gil-i Makhtūm* (silicate of alumina), 273 mg Kāfūr (*Cinnamomum camphora* (L.) J. Presl), and 273 mg *Za'frān* (*Crocus sativus* L.). This mixture should be kneaded in rose water and vinegar before application [11].

Tukhm-i Turb Paste: *Tukhm-i Turb* (*Raphanus sativus* L.) can be used as a paste with *Khar Mohra Muharriq* (burnt *Cyprea moneta* L.). This is beneficial in Kalaf when combined with *Sanā* (*Senna alexandrina* Mill.), *Suhaga* (sodium borate), *Kishmish* (*Vitis vinifera* L.), *Karam Kalla* (*Brassica oleracea* L.), and *Kakṛī* (*Cucumis melo var. flexuosus*. (L.) Naudin.) [42,76].

Application of *Jālī* and *Muḥallil Advia*: The use of *Jālī* (skin cleansing agents) and *Muḥallil* (resolvent) drugs such as *Bādām Talkh* (*Prunus amygdalus* var. *amara*), *Būra Armani* (silicates of alumina), *Dārchīnī* (*Cinnamomum verum* J. Presl.), *Filfil Siyāh* (*Piper nigrum* L.), *Kundush* [*Centipeda minima* (L.) A. Br. & Asch.], *Qust* [*Saussurea auriculata* (DC.) Sch. Bip.], *Tukhm-i-Jarjīr* [Eruca vesicaria (L.) cav.], *and Tukhm-i Turb* (*Raphanus sativus* L.), has been advised as beneficial in treating Kalaf [52].

Topical Application with Post Kadū Shīrīn: A topical application consisting of Post *Kadū Shīrīn* [*Lagenaria siceraria* (Molina) Standl.] ground in *Sirka* (acetic acid) and *Kaf-i Dariyā* (*Sepia offcinalis* L.) rubbed in *Āb-i-Līmū* (*Citrus limon* L. juice) is also advised in Kalaf [54, 55].

Other Topical Therapy Options: Various potent medications can be applied to the affected areas, including the dust of *Āqarqarḥā* [*Anacyclus pyrethrum* (L.) Lag.], *Chūna* (lime), *Gandhak Āmla Sār* (purified sulphur), *Hartal Zard* (arsenic trisulphide), *Kāth* [*Acacia leucophloea* (Roxb.) Willd.], *Qirdmānā* [*Bunium persicum* (Boiss.) B.Fedtsch], *Mushktarāmashī'* (*Mentha pulegium* L.), *Rā'ī* [*Brassica nigra* (L.) K. Koch], *Taj* [*Cinnamomum cassia* (L.) J. Presl.], *Tukhm-i Utangan* [*Blepharis edulis* (Forssk.)Persl.], *Tukhm-i Lūt* (*Quercus incana* Bartram), *Zīra* (*Carum carvi* L.), and *Zarāwand* (*Aristolochia fontanesii* Boiss & Reuter.) [50].

3.3.9.2.4. Special recommendations by Unani scholars

Ibn Sina's approach: Ibn Sina recommends *Natūl* (irrigation) with repeated applications of *Shiyāf-i Mur* (suppository of *Commiphora myrrha*) and *Shiyāf Bardi*. This method is considered effective in the early stages of Kalaf to address decreased blood flow [48]. Additionally, applying Anjīr (*Ficus*

carica L.) soaked in vinegar can resolve stored morbid blood beneath the skin [42]. He also advocates using fine *Husn-i Yusuf* (*Rubia tinctoria* Salisb.) powder with Roghan-i Chanbelī (*Jasminum officinale* L.) or butter [55].

Razi's approach: Razi emphasized avoiding substances that induce facial congestion and recommended topical applications of *Bāqlā* (*Vicia faba* L.) and *Tukhm-i Tarbūz* [*Citrullus lanatus* (Thunb.) Mats. & Nakai] in the form of *Ṭilā* (anointment). He also advocated for leeching and specific *Ṭilā* prepared from *Tukhm-i Māzaryūn* (*Daphne mezereum* L.) [75].

Hakim Hafiz Jalil's reference to Tabri: Hakim Hafiz Jalil refers to a prescription by Tabri, suggesting the application of a mixture of fine powder of *Bāqlā* (*Vicia faba* L.), *Katīrā* [*Cochlospermum religiosum* (L.) Alston], *Anzarūt* (*Astragalus sarcocolla* Dymock), and *Maṣṭagī Rūmī* (*Pistacia lentiscus* L.) in *Safedi Bayza-i Murgh* over the face as needed [42].

Ahmad Bin Tabri's method: Ahmad Bin Tabri prefers *Mulayyin* (laxative) agents over *Dāfi'-i Sakhn Advia* (calorific resolving drugs) in Kalaf. He also describes the use of seawater in Basra for treating Kalaf [73].

Al-Mansūri's medications: Al-Mansūri recommends grinding and applying medications such as Badam Talkh (*Prunus amygdalus* var. amara), *Tukhm-i Kharpaza* (*Cucumis melo* L.), *Tukhm-i Turb* (*Raphanus sativus* L.), and *Ārad-i Bāqlā* (*Vicia faba* L.) to affected areas [45].

Ibn Hubal Baghdadi's recommendation: Ibn Hubal Baghdadi advises applying a paste *of Bādām Shīrīn Muqasshar* (*Prunus amygdalus Batch*.), *Būra Armani* (silicates of alumina), *Tukhm-i Turb* (*Raphanus sativus* L.) and *Luāb-i Methī* (mucilage of *Trigonella foenum-graecum* L.) after taking a Hammām (bath). He also suggests applying soap until a burning sensation develops, followed by *Roghan-i-Bādām* (almond oil) or *Roghan-i Gul* (oil of *Rosa damascena* Mill.) [50,77].

Rabban Tabri's Tablets: Allama Rabban Tabri mentions tablets prepared with *Bāqlā* (*Vicia faba* L.), *Katīrā* [*Cochlospermum religiosum* (L.) Alston], *Anzarūt* (*Astragalus sarcocolla* Dymock.), and *Maṣṭagī Romī* (*Pistacia lentiscus* L.) for cleansing the skin and improving complexion in Kalaf. He also suggests applying roasted *Natrūn* (bromide salt of sodium) and *Būra Armani* (silicates of alumina) mixed with '*Aṣl*' [42].

Majūsi's Recommendation: Majūsi advises using *Tukhm-i Turb* (*Raphanus sativus* L.) with '*Asl* in Kalaf and applying a paste of *Dawa-i Filfil* (*Piper longum* L.) and *Būra Armani* on the affected area [11].

Allama Antaki's Opinion on Pregnancy: Allama Antaki believes that if Kalaf is noticed in pregnant women, treatment should be delayed until after delivery, as the condition often resolves postpartum [42].

3.3.9.2.5. Dietary recommendations

The prescribed dietary recommendations encompass the incorporation of *Mā' al-Jubn* (cheese water), a dietary element that holds potential benefits in the treatment process of Kalaf. Conversely, certain dietary restrictions are imperative to adhere to, which involve the avoidance of *Muwallid-i Sawdā Aghziya* (diets promoting the production of black bile) and prolonged consumption of eggs, as these dietary practices have the potential to exacerbate the condition [71].

3.3.10. Research Investigating Unani Treatments for Melasma

Recent investigations into the clinical efficacy and safety of various traditional Unani medicines have been conducted. Table **1** delineates the essential particulars of the clinical trials that have been reported, while Table **2** enumerates the clinical trials currently underway, as documented in the clinical trial registry of India.

Table 1. Summary of clinical trials conducted on several Unani medications.

S. No.	Unani Drug(s)	Study ID, Year, Trial Design	Sample Size and Duration	Type of Melasma	Comparator	Outcome
1	Tila-e-Kalaf was prepared by combining equal proportions of finely powdered *Lens culinaris* and *Prunus amygdalus var. amara*. This mixture was then combined with a sufficient amount of *Ficus carica* decoction to create a homogenous paste.	Salma *et al*., 2023 Open label RCT[78]	Test = 28 Control = 27 Duration = 8 weeks	Epidermal melasma	Hydroquinone 4% Topically	Tila-e-Kalaf and hydroquinone 4% were statistically equally effective treatment for melasma.
2	Topical use of the powdered Unani formulation consisting of *Lupinus albus* L., *Eruca sativa* Mill., *Aucklandia lappa* DC, *Prunus amygdalus* Stokes, *Commiphora mukul* (Hook. ex Stocks) Engl, *Piper nigrum* L., *Carthamus tinctorius* L., borax and honey.	Qaiyyum *et al*., 2021, Open label RCT[79]	Test = 30 Control = 30 Duration = 8 weeks	Epidermal, dermal and mixed type of melasma	Hydroquinone 4% Topically	Unani classical formulation and the control drug hydroquinone (4%) were equally effective treatment for melasma.

(Table1) contd….

S. No.	Unani Drug(s)	Study ID, Year, Trial Design	Sample Size and Duration	Type of Melasma	Comparator	Outcome
3	Traditional medicinal product consisting of extracts of *C. aritinum* L. and C. melo var. inodorus H. Jacq seed. prepared as a cream.	Mahjour *et al* 2019, triple blinded RCT [80]	Test = 32 Control = 32 Duration = 12 weeks	Melasma (all types)	Hydroquinone 4% Topically	There was no difference between the efficacy of Traditional medicine cream and hydroquinone 4%.
4	Powdered cuttlefish bone and lemon juice topically along with oral *Cascuta reflexa* capsule.	Sultana *et al* 2012, Randomized placebo controlled trial [81]	Test = 20 Control = 20 Duration = 8 weeks	Melasma (all types)	Oral Placebo Capsule with Same Topical Application	Interventions had promising effects in melasma.
5	Zimad (semisolid paste) was made by powdered seeds of *Raphanus sativus* and *Apium graveolens* with sugarcane vinegar.	Gauri *et al* 2015, Single blind RCT [82]	Test = 20 Control = 20 Duration = 45 days	Melasma (all types)	Azelaic acid 10% cream	Zimad was equally efficacious to standard drug in ameliorating the lesions of Melasma
6	Coded Unani formulations MN and XM for oral administration and local application, respectively.	Latif *et al* 2012, Single blind Placebo Controlled Trial [83]	Test = 21 Control = 21 Duration = 12 weeks	Moderate to severe melasma (all types)	Placebo formulations MP and XP for oral administration and local application, respectively.	The response of the combination therapy was better than placebo.
7	*Nigella sativa* with vinegar	Zarnigar 2011, Single-arm clinical trial [84]	Test = 20	Melasma (all types)	None	The response of the test drugs was satisfactory.

Table 2. Summary of clinical trials in progress on several Unani medications.

S. No.	Unani Drug(s)	Principal Investigator (s) and Trial Design	Sample Size and Duration	Type of Melasma	Comparator	CTRI Reg. No. (if Available)
1	Zimaad-e-Baras consisting of *Ficus carica, Psoralea corylifolia, Cleome icosandra Syn. C. viscosa, Zingiber zerumbet* and *Citrus limon.*	Rahman, R., Faisal A., Nawab M. and Parveen S.N. Single-arm multicentric clinical trial	Test = 300 Duration = 8 weeks	Epidermal, dermal and mixed type of melasma	None	CTRI/2015/11/006385
2	*Prunus amygdalus* var. *amara* with vinegar	Sheikh S. RCT	Test and control = 40 Duration = 8 weeks	Melasma (all types)	Hydroquinone 4% topically	CTRI/2021/03/032310
3	Decoction of *Cuscuta reflexa* and topical application of *Saussurea lappa* with honey.	Fatima T. RCT	Test and control = 36 Duration = 60 days	Melasma (all types)	Tranexamic acid orally and azelaic acid cream locally	CTRI/2021/03/032083
4	Zimad of Unani formulation (ingredients are not mentioned on CTRI)	Fatima T. RCT	Test and control = 60 Duration = 8 weeks	Melasma (all types)	Hydroquinone 4% topically	CTRI/2021/09/036582

(Table 2) contd….

S. No.	Unani Drug(s)	Principal Investigator (s) and Trial Design	Sample Size and Duration	Type of Melasma	Comparator	CTRI Reg. No. (if Available)
5	Haleela Siyah Tukhme Turb and Tukhme Jarjir	Zulfar TH. Randomized comparative study	Test and control = 44 Duration = 28 days	Melasma (all types)	Haleela Siyah Ard Baqla and Tukhme Kharpazah	CTRI/2022/04/041617
6	Mixture of *Qust Shireen* and honey	Khan N. Randomized comparative study	Test and control = 80 Duration = 56 days	Melasma (all types)	Mixture of *Qust Shireen* and honey along with R.F.	CTRI/2022/10/046862
7	*Raphanus sativus* seed extract with honey	Horti A. RCT	Test and control = 40 Duration = 8 weeks	Melasma (all types)	Hydroquinone 4% topically	CTRI/2022/07/044080
	Powdered Rewand chini with honey	Swaleha W. RCT	Test and control = 37 Duration = 42 days	Melasma (all types)	Hydroquinone 2% topically	CTRI/2022/07/044251

4. DISCUSSION

The Unani system of medicine, deeply rooted in a rich and illustrious history, has been a cornerstone in the promotion of health, the implementation of preventive measures, and the management of various diseases. This system employs a comprehensive approach that is grounded in the use of time-tested drugs and therapies, which have been honed over centuries of practice. Unani practitioners, in particular, have been addressing conditions such as melasma through a multi-faceted approach that includes *'Ilāj bi'l Dawā'* (pharmacotherapy), *'Ilāj bi'l Ghidhā'* (diet therapy), and *'Ilāj bi'l-Tadbīr'* (regimenal therapy). These methods, while traditional, still require validation and exploration within the context of contemporary, conventional medicine to ensure their efficacy and safety. For this purpose, numerous clinical investigations have been conducted on a variety of Unani formulations, both single and compound in nature. These studies have demonstrated promising results in the treatment of melasma (Table **1**). However, it is important to note that these studies have significant limitations that need to be addressed in future research. For instance, many of these studies employed the use of liniments or semi-solid pastes composed of crude drug powder, or they involved the direct mixing of powder with vinegar. These methods, while traditional, may not provide the most accurate representation of the drug's potential efficacy.

Furthermore, these studies often lacked crucial elements such as drug identification or chemical fingerprinting, which are essential for understanding the exact composition and potential interactions of the drugs being used. In a limited number of studies, plant drug extracts were utilized, and recurrence assessments were also conducted. These elements add a layer of depth to the research but are not consistently present across all studies.

Therefore, to fully elucidate the impact of these traditional medications on the treatment of melasma and to substantiate the claims made by ancient Unani physicians, further research is needed. These studies should ideally take the form of well-structured, comprehensive randomized controlled trials. These trials would provide a more robust and reliable understanding of the efficacy, safety, and potential applications of Unani treatments in the context of melasma and potentially other similar conditions.

The present work aims to serve as a foundational resource for understanding the etiology, pathophysiology, diagnosis, and treatment approaches of melasma, based on the insights and wisdom of Unani scholars, in addition to incorporating findings from recent clinical trials. It is our hope that this work will inspire and guide further research in this area, contributing to the advancement of both traditional and modern medical practices.

CONCLUSION

This comprehensive review endeavors to encapsulate the intricate details of melasma as understood in the Unani system of medicine. The analysis postulates the potential pathogenesis of melasma, drawing from the wisdom and descriptions provided by ancient scholars. This review not only illuminates the treatment methodologies employed in Unani medicine but also underscores the potential systemic and topical treatment options that could be further validated through rigorous scientific methodologies. Moreover, it provides a succinct summary of both completed and ongoing clinical trials focused on the treatment of melasma within the context of Unani medicine. This review may serve as a reference point for future research, enabling the planning of subsequent studies on this disease with a comprehensive understanding of the previous investigations conducted in this field.

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CONFLICT OF INTEREST

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REFERENCES

[1] Cosmetic Dermatology. *Cosmetic Dermatology For Skin Of Color*; McGraw Hill Education, **2009**.

[2] Wolff, K; Fitzpatricks Color Atlas, J.R. *Fitzpatricks Color Atlas and Synopsis of Clinical Dermatology*; McGraw Hill Education, **2009**, pp. 344-346.

[3] Gawkrodger, D.; Ardern-Jones, M.R. *Dermatology An Illustrated Colour Text*, 6th ed.; Elsevier: New York, **2017**.

[4] Raihan, A.; Kumaran, M.S. Study of contact sensitivity to cosmetic allergens in melasma. *Pigment Int.*, **2019**, *6*, 34-36.

[5] Rashmi, S. *Melasma A Monograph*; Jaypee brothers: New Delhi, **2015**.

[6] Jackson-Richards, D.; Pandya, A.G., Eds.; *Dermatology for Skin of Color*; Springer: New York, **2014**, pp. 27-31.

[7] Passeron, T.; Ortonne, J. *Atlas of Pigmentary Disorders*; Adis Cham, **2016**. http://dx.doi.org/10.1007/978-3-319-10897-1

[8] Busam, K.J. *Dermatopathology*; Elsevier Saunders: USA, **2016**, p. 270.

[9] Goldman, L.; Ausiello, D.A. *Cecil Textbook of Medicine*; ELsevier, **2004**.

[10] Shah, S.N. *API Text Book of Medicine*; The Associatio of Physicians of India: Mumbai, **2012**.

[11] Majoosi, A.H.A.I.A. *(Urdu translation by Kantoori GH). Kamilus Sana; Vol-2*; Idara Kitabul Shifa: New Delhi, **2010**.

[12] Jain, S. *Dermatology Illustrated Study Guide and Comprehensive Board Review*; Springer: New York, **2012**, p. 137.

[13] Baumann, L; Saghari, S *Cosmetic Dermatology Principles and Practice*; McGraw Hill Education, **2009**.

[14] S, B. *Oxford Handbook of Medical Dermatology*; Oxford University Press: UK, **2016**, p. 583.

[15] Freedberg, I.M.; Eisen, A.Z.; Wolff, K.; Austen, K.F.; Goldsmith, L.A.; Fitzpatricks Dermatology, K.S.T. *General Medicine*; McGraw Hill Education: USA, **2003**, pp. 977-978.

[16] Grimes, P.E. Management of hyperpigmentation in darker racial ethnic groups. *Semin. Cutan. Med. Surg.*, **2009**, *28*(2), 77-85. http://dx.doi.org/10.1016/j.sder.2009.04.001 PMID: 19608057

[17] Suryakant, B.; Samipa, A.; Mukherjee, S.; Pralhadrao, B. Dermoscopy - histopathology correlation. In: *Dermoscopy - Histopathology Correlation*; Ankad, B.S.; Nikam, B.P.; Mukherjee, S.S., Eds.; Springer Nature: Singapore, **2021**; pp. 163-183.

[18] Wetter, D.A. Dermatology for Skin of Color. In: *Mayo Clinic Proceedings*; , **2014**.

[19] Nicolaidou, E.; Antoniou, C.; Katsambas, A.D. Origin, clinical presentation, and diagnosis of facial hypermelanoses. *Dermatol. Clin.*, **2007**, *25*(3), 321-326, viii. http://dx.doi.org/10.1016/j.det.2007.05.002 PMID: 17662897

[20] Kang, H.Y.; Ortonne, J.P. What should be considered in treatment of melasma. *Ann. Dermatol.*, **2010**, *22*(4), 373-378. http://dx.doi.org/10.5021/ad.2010.22.4.373 PMID: 21165205

[21] Torres-Álvarez, B.; Mesa-Garza, I.G.; Castanedo-Cázares, J.P.; Fuentes-Ahumada, C.; Oros-Ovalle, C.; Navarrete-Solis, J.; Moncada, B. Histochemical and immunohistochemical study in melasma: Evidence of damage in the basal membrane. *Am. J. Dermatopathol.*, **2011**, *33*(3), 291-295. http://dx.doi.org/10.1097/DAD.0b013e3181ef2d45 PMID: 21317614

[22] Miot, L.D.; Miot, H.A.; Polettini, J.; Silva, M.G.; Marques, M.E. Morphologic changes and the expression of alpha-melanocyte stimulating hormone and melanocortin-1 receptor in melasma lesions: A comparative study. *Am. J. Dermatopathol.*, **2010**, *32*(7), 676-682. http://dx.doi.org/10.1097/DAD.0b013e3181cd4396 PMID: 20534990

[23] Bandyopadhyay, D. Topical treatment of melasma. *Indian J. Dermatol.*, **2009**, *54*(4), 303-309. http://dx.doi.org/10.4103/0019-5154.57602 PMID: 20101327

[24] Farshi, S. Comparative study of therapeutic effects of 20% azelaic acid and hydroquinone 4% cream in the treatment of melasma. *J. Cosmet. Dermatol.*, **2011**, *10*(4), 282-287. http://dx.doi.org/10.1111/j.1473-2165.2011.00580.x PMID: 22151936

[25] Kaliterna, D. Melasma review of current treatment modalities and efficacy assessment of a new resorcinol-based topical formulation. *Glob. Dermatol.*, **2017**, *2017*(4), 1-6.

[26] McKesey, J.; Tovar-Garza, A.; Pandya, A.G. Melasma treatment: An evidence-based review. *Am. J. Clin. Dermatol.*, **2020**, *21*(2), 173-225. http://dx.doi.org/10.1007/s40257-019-00488-w PMID: 31802394

[27] Prignano, F.; Ortonne, J.P.; Buggiani, G.; Lotti, T. Therapeutical approaches in melasma. *Dermatol. Clin.*, **2007**, *25*(3), 337-342, viii. http://dx.doi.org/10.1016/j.det.2007.04.006 PMID: 17662899

[28] Gupta, A.K.; Gover, M.D.; Nouri, K.; Taylor, S. The treatment of melasma: A review of clinical trials. *J. Am. Acad. Dermatol.*, **2006**, *55*(6), 1048-1065. http://dx.doi.org/10.1016/j.jaad.2006.02.009 PMID: 17097400

[29] Khatoon, F.; Husain, N.; Jabeen, A.; Uddin, Q.; Azahar, M.; Qureshi, A.; Khan, A.A. Psoriasis with special reference to Unani medicine - A review. *Open Health*, **2022**, *3*(1), 124-140. http://dx.doi.org/10.1515/openhe-2022-0024

[30] Khatoon, F.; Azahar, M.; Jabeen, A.; Uddin, Q.; Husain, N.; Naikodi, M.A.R. Treatment of chronic plaque psoriasis with herbal Unani formulations: A randomized control trial of efficacy and safety. *J. Ethnopharmacol.*, **2022**, *296*, 115456. http://dx.doi.org/10.1016/j.jep.2022.115456 PMID: 35724745

[31] Doni, M.; Patel, M.I.; Khalid, M.; Husain, N.; Khan, M.Q.; Ayesha, B. Therapeutic evaluation of herbal formulation in acne vulgaris and its influence on quality of life-A single-arm clinical trial. *J. Herb. Med.*, **2022**, *34*, 100577. http://dx.doi.org/10.1016/j.hermed.2022.100577

[32] WHO Global Centre for Traditional Medicine. Available from:https://www.who.int/initiatives/who-global-centre-for-traditional-medicine (Accessed Aug 6, 2023).

[33] CCRUM. *Unani System of Medicine: The Science of Health and Healing*; department of ayUSH ministry of Health & family Welfare, **2013**.

[34] Ahmad, W.; Sofi, G.; Alam, M.A.; Zulkifle, M.; Ahmad, B. Understanding Holism in the light of principle underlying practice of Unani Medicine. *Rev. Environ. Health*, **2022**, *37*(2), 189-199. http://dx.doi.org/10.1515/reveh-2021-0009 PMID: 33984879

[35] Schmidt-Stiedenroth, K. *Unani Medicine in the Making*; Amsterdam University Press, **2020**.

[36] Husain, N.; Khalid, M. Aesthetic significance of solah shringar (sixteen ornaments) in unani medicine. *J. Complement. Altern. Med. Res.*, **2021**, 69-81.

[37] Kapur, M. Basic principles of unani system. In: *Psychological Perspectives on Childcare in Indian Indigenous Health Systems*; Springer India: New Delhi, **2016**; pp. 89-95. http://dx.doi.org/10.1007/978-81-322-2428-0_7

[38] Imran, S.; Khalid, M.; Husain, N.; Khan, M.Q.; Shaikh, S. The efficacy of topical marham-e-akbar in chronic atopic dermatitis - an open-label interventional study. *Drug Metab. Pers. Ther.*, **2022**.

[39] Husain, N.; Uddin, Q.; Kazmi, M.H.; Khalid, M. A non-inferiority randomized controlled clinical trial comparing Unani formulations and PUVAsol in non-segmental vitiligo. *J. Complement. Integr. Med.*, **2023**, *20*(1), 250-257. http://dx.doi.org/10.1515/jcim-2021-0057 PMID: 34162019

[40] Jagannathan, M.; Sadagopan, K.; Ekkarakudy, J.; Anandan, H. Clinico-epidemiological study of patients with melasma in a tertiary care hospital - A prospective study. *Int. J. Sci. Stud.*, **2017**, *4*, 117-120.

[41] Tabri, R. *Firdausul Hikmat*; Idara Kitabul Shifa: New Delhi, **2010**.

[42] Ahmad, H.H.J. *Tazkira Tu Jaleel*; CCRUM, Ministry of Health and Family Welfare, **2008**.

[43] Tabri, A.M. *Moalajat-e Buqratiya*; CCRUM, Ministry of Health and Family Welfare, **1995**.

[44] Razi, A.M.B.Z. Al Hawi Fil Tib-Vol. 23 (Urdu); Saba Publishers, Aligarh, **1994**.

[45] Quamri, A.M.H. *Ghina Muna Ma Tarjuma Minhajul Ilaj*; CCRUM: New Delhi, Ministry of Health and Family Welfare, **2008**.

[46] Majoosi, A. *Kamilus Sana*; CCRUM, Ministry of Health and Family Welfare, **2010**.

[47] Shirbeigi, L.; Ranjbar, M. "Vascular Etiology of Melasma" the idea which was first presented by avicenna and rhazes. *Tradit. Integr. Med.*, **2016**, 166-167.

[48] Sina, I. *Al Qanoon Fil Tib*; Idara Kitabul Shifa: New Delhi, **2010**.

[49] Zohar, I. *Kitabul Taisir Fil Mudawat Wat Tadbir*; Ministry of Health and Family Welfare, **1986**.

[50] Baghdadi, I.H. *Kitabul Makhtarat Fil Tib*; CCRUM, Ministry of Health and Family Welfare, **2007**.

[51] Jurjani, I. *Zakheera Khawarzam Shahi*; Idara Kitabul Shifa, **2010**.

[52] Rizwan, H.K.A. *Tarjuma Sharah Asbab*; CCRUM, Ministry of Health and Family Welfare,Govt of India, **2010**.

[53] Arzani, MA. Tibbe Akbar Urdu; Matba Nami Munshi Nawal Kishor, Lucknow, 1870.

[54] Khan, M.A. *Akseere Azam*; Idara Kitabush Shifa: New Delhi, **2011**.

[55] Khan, H. *Ajmal. Haziq*; Madina Publication: Karachi, **1983**.

[56] kabiruddin, M. *Bayaz e Kabir*; Idara Kitabul Shifa: New Delhi, **2010**.

[57] Handel, A.C.; Miot, L.D.B.; Miot, H.A. Melasma: A clinical and epidemiological review. *An. Bras. Dermatol.*, **2014**, *89*(5), 771-782. http://dx.doi.org/10.1590/abd1806-4841.20143063 PMID: 25184917

[58] Alexis, A.F. Skin of Color. In: *A practical guide to dermatologic diagnosis and treatment*; Springer, **2013**.

[59] Trivedi, M.K.; Yang, F.C.; Cho, B.K. A review of laser and light therapy in melasma. *Int. J. Womens Dermatol.*, **2017**, *3*(1), 11-20. http://dx.doi.org/10.1016/j.ijwd.2017.01.004 PMID: 28492049

[60] Khanna, N. *Illustrated synopsis of dermatology & sexually transmitted diseases*; Elsevier, **2011**.

[61] Mette Henriksen, R. Objective Determination of Fitzpatrick Skin Type. *Dan Med Bull.*, **2010**, *57*(8), B4153.

[62] Ortonne, J.P.; Arellano, I.; Berneburg, M.; Cestari, T.; Chan, H.; Grimes, P.; Hexsel, D.; Im, S.; Lim, J.; Lui, H.; Pandya, A.; Picardo, M.; Rendon, M.; Taylor, S.; Van Der Veen, J.P.W.; Westerhof, W. A global survey of the role of ultraviolet radiation and hormonal influences in the development of melasma. *J. Eur. Acad. Dermatol. Venereol.*, **2009**, *23*(11), 1254-1262. http://dx.doi.org/10.1111/j.1468-3083.2009.03295.x PMID: 19486232

[63] Nayak, C.S.; Nouveau, S.; Agrawal, D.; Kohli, M.; Bernerd, F.; Misra, N. Skin hyperpigmentation in Indian population: Insights and best practice. *Indian J. Dermatol.*, **2016**, *61*(5), 487-495. http://dx.doi.org/10.4103/0019-5154.190103 PMID: 27688436

[64] Bhura, M.; Sharma, S. A clinico-epidemiological study on melasma: A prospective observation. *Int. J. Health Clin. Res.*, **2021**, *4*(3), 61-63.

[65] Standard Unani Medical Terminology. *Central Council For Research in Unani Medicine*; New Delhi, **2012**.

[66] Chandpuri, K. *Mojizul Quanoon*; Qaumi Council Bara-e Faroog-e Urdu Zaban: New Delhi, **1998**.

[67] Mojtabaee, M.; Mokaberinejad, R.; Adhami, S.; Mansouri, P.; Rahbar, M. Nutritional advice for patients with melasma in iranian traditional medicine. *J. Ski. Stem Cell.*, **2016**, 3.

[68] Verma, K.; Kumre, K.; Sharma, H.; Singh, U. A study of various etiological factors in the causation of melasma. *Indian J. Clin. Exp. Dermatol.*, **2015**, *1*, 28-32.

[69] Ahmad, SMR Review on melasma with special reference to treatment in unani medicine. *Int. Pharm. Sci.*, **2013**, 42-54.

[70] Aquil, Z.; Khalid, M.; Uddin, Q. Potential role of unani medicinal plants in management of kalaf (Chloasma): A review. *J. Skin*, **2019**, *3*(1), 1-3.

[71] Jamil, S.S.; Siddiqui, S.A.; Fazil, M. *Standard Unani Treatment Guidelines for Common Diseases*; Central Council for Research in Unani Medicine (CCRUM), **2014**.

[72] Razi, Z. *Kitabul Hawi*; *VOL 21 par*; CCRUM: New Delhi, **2007**.

[73] Tabri, A.M. *Moalajat Buqratiya*; CCRUM, Ministry of Health and Family Welfare, **1995**.

[74] Mushtaq, S.; Sultana, A.; Nikhat, S.; Rehman, M. Concept of systemic cleansing through concoctives and purgatives (Munzij Mushil Therapy) as a regimen in chronic diseases. *J. Med. Erud.*, **2014**, *2*, 28-35.

[75] Razi, Z.; *Kitabul Fakhir Fit Tib; Vol-1*; CCRUM: New Delhi, **2008**.

[76] Antaki, D. *Tazkirah Oolil Albab*; CCRUM, Ministry of Health and Family Welfare, **2010**.

[77] Khatoon, F.; Azahar, M.; Uddin, Q.; Husain, N.; Moin, M.S.; Khan, S. A comprehensive review on Trigonella foenum-graecum L. with special reference to Unani medicine. *Comb. Chem. High Throughput Screen.*, **2023**. PMID: 37143276

[78] ShamsiY.Clinical evaluation of a topical unani pharmacopoeial formulation tila-e-kalf in the management of melasma (Kalf): A randomized controlled clinical trial. *Orig. Res. Artic. AJP*, **2022**, *13*, 255-264.

[79] Qaiyyum, I.A.; Nawab, M.; Kazmi, M.H. A randomized controlled clinical trial to evaluate safety and efficacy of a Unani formulation in the management of Kalaf (Melasma). *J. Complement. Integr. Med.*, **2023**, *20*(1), 233-240. http://dx.doi.org/10.1515/jcim-2021-0353 PMID: 34582636

[80] Mahjour, M.; Banihashemi, M.; Rakhshandeh, H.; Vakili, V.; Khoushabi, A.; Kakhki, M.T. A triple-blind, randomized trial of a traditional compound as compared to 4% hydroquinone in melasma. *J. Herb. Med.*, **2020**, *19*, 100308. http://dx.doi.org/10.1016/j.hermed.2019.100308

[81] Sultana, A.; Siddiquee, R.A.; Khanna, N.; Ahmad, T.; Shiffa, M. Comparative clinical evaluation of unani formulations in the treatment of melasma. *Am. J. PharmTech Res.*, **2012**, 2.

[82] Gauri, M.; Ahmed, T.; Khan, M.S.; Ali, S.J. Therapeutic evaluation of unani herbal medicine for topical application (zimad of tukhme turb, tukhme karafs and sirka) in melasma (Kalaf) - A single blind randomized controlled study. *Int. J. Sci. Res.*, **2015**, *4*, 38-41.

[83] Abdul-Latif, Z. Randomized clinical trial of unani formulations in chloasma/melasma. *Hippocrat. J. Unani Med.*, **2012**, *7*, 19-31.

[84] ZarnigarR.Evaluation of shooneez (Nigella Sativa) and sirka (Sugarcane Vinegar) in kalaf (Melasma). *Hippocrat. J. Unani Med.*, **2011**, *6*, 145-149.