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A study of potential risk factors of *Shvitra* (vitiligo): a case-control pilot study

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Prevalence of vitiligo in India varies from 0.6% to 1.13% with a high prevalence of up to 8.8% in Gujarat and Rajasthan. It is a major skin disease in public health domain globally. There are many theories behind pathogenesis of vitiligo but autoimmunity is considered as the most crucial trigger, however exposure factors and their association with development of diseases as risk factor largely remain unknown. This study is conducted to assess the role of etiological factors mentioned in Ayurveda literature as risk factor in manifestation of *Shvitra* (vitiligo). The present study is a case-control study where 80 cases (vitiligo) and 80 controls (healthy) were selected, examined and interrogated for assessment of exposure of *viruddha ahara* through a validated questionnaire and their blood samples were investigated. Total 93 exposure factors were assessed, of which 47 were found with significant odds ratio in univariate analysis. In subgroup multivariate analysis, 2 of 15 domains assessed showed significant odds namely *Vega dharana* (OR: 35.4, 95% CI: 1.54-827.0) and *Papa karma* (OR: 15.78, 95% CI: 1.25- 199.5). *Shvitra* severity score (SSS) is found positively correlated (r=0.62, p<0.01) with Hs-CRP and also with total *viruddha ahara* score (r=0.96, p<0.01). This case-control analytical study provides evidence that *vega-dharana* and *Papakarma* are the major determinants of *Shvitra* as described by Acharya Charak. Future prospective studies with larger sample size are warranted to validate this finding and develop preventive and treatment strategies for broader application.

Keywords: Bio-chemical markers, Case-control study, *Papakarma, Shvitra* (vitiligo), *Vegadharna, Viruddha ahara*

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The vitiligo was ranked one of the major medical problems of India because it is a psychologically devastating and frequently recalcitrant skin disorder[1]. Vitiligo is characterized by autoimmune destructions of melanocytes that consequences in depigmented patches of skin and mucosal surfaces. Oxidative stress may play a major role in pathogenesis of vitiligo (*Shvitra-as* in Ayurveda) Study revealed the prevalence of vitiligo varies from 0.6% to 1.13% [mean 1.1±0.68] in the population-based surveys[2-5] and in the hospital-based surveys the range was wider [0.43%-9.98%, mean 2.96±0.99][6-8]. Overall prevalence was 2.51±0.49[9] with high prevalence up to 8.8% in Gujarat and Rajasthan[10]. Thus variation is expected to be due to dietary and lifestyle factors, which may be accepted as risk factors in development of disease. However, the determinant factors of disease could also include host related viral genetic variations[11]. It is observed that 16-35% of patients with vitiligo experience significant psychiatric morbidity, depression (10%), dysthymia (7-9%), sleep disturbances (20%), suicidal thoughts (10%), suicidal attempts (3.3%) and anxiety (3.3%)[12]. Vitiligo can also lead to difficulties in forming relationships, avoidance of certain social situations and difficulties in sexual relationships[13]. Diet with wrong food combinations, including incorrect processing, incorrect quantity consumed in inappropriate way at inappropriate time and in wrong season can be considered as *Viruddha Ahara.* Etiological factors for *Shvitra* according to Ayurveda are mainly based on human behaviour pattern related to food incompatibility and stress which can be modified and changed when there is well established correlation between these risk factors and outcomes. As per Ayurveda every person has own particularized psychological and physiological constitutions, which is affected by diet and life-style[14]. If dietic rules are not followed as described in Ayurveda under *viruddha aahar* (incompatible foods)

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such practice can lead to various diseases like impotency, erysipelas, blindness, ascites, bullous, insanity, fistula in ano, coma or fainting, intoxication, abdominal distention, stiffness in neck, varieties of anaemia, indigestion, various skin diseases, diseases of intestines, swelling, gastritis, fever, rhinitis, and infertility[15].

Various studies have focused on epio-demographic pattern, clinical profile of disease but none to the best of our knowledge emphasized on dietary pattern and its impact on biochemical markers to assess inflammation *i.e.,* Hs-CRP and Serum Insulin which are observed to be raised[16,17]. Exact aetiopathogenesis of vitiligo is still a big challenge to medical fraternity. So present study was undertaken to identify exposure status of risk factors based on dietary incompatibility (*Viruddha aahara*) and to find out the strength of their association with *Shvitra* (vitiligo). Based upon finding an insight may be developed to understand pathology and to develop guidelines for rational therapeutic management. This case-control study is an attempt to explore risk factors of *Shvitra*.

Materials and Methods

This study was conducted during November 2021 to march 2022, after Institutional Ethics Committee (IEC) approval (IEC-AIIA/2020-PG-189) and Clinical Trials Registry - India (CTRI) (CTRI/2021/02/030941). A total of 160 subjects at AIIA-OPD were enrolled which included 80 patients with *Shvitra* (vitiligo) and 80 healthy as control. The control were sex and age-matched (closest possible) non-vitiligo and healthy. *Shvitra* (Vitiligo) cases were clinically classified as per the ayurvedic literature. Participants were asked for last one year exposure with sufficient time provided. Memory impairment, cognitive function impairment was excluded to avoid recall bias. To reduce interviewer bias, all the interviews were conducted by the same researcher.

Sample size calculation:

Sample size (n) = $(r + 1) / r \times p (1 - p) (Z_{1-\beta} + Z_{1-a/2})^2 / (p_1 - p_2)^2$

n = Desired number of samples

r = Control to cases ratio (1 if the same number of subjects in both groups)

p = Proportion of population = $(P_1 + P_2) / 2$

$Z_{1-\beta}$ = It is the desired power (0.84 for 80% power and 1.28 for 90% power)

$Z_{1-a/2}$ = Critical value and a standard value for the corresponding level of confidence.

(At 95% CI or 5% type I error, it is 1.96, and at 99% CI or 1% type I error, it is 2.58)

P_1 = Proportion in cases (0.7)

P_2 = Proportion in controls (0.6)

N= 80 in each group

Inclusion-exclusion criteria

Patient (case) between age of 18 to 60 years presenting with symptoms of *Shvitra* (vitiligo), *i.e, Araktaloma* (~Hair not discolored / no depigmentation of hair), *Tanu* (~Thin/superficial lesion), *Yat Pāṇḍu* (~Whitish or pale patch), *Nātichirotthitam* (~Recently manifested), *Madhyāvakāśe* (~Having limited spread), *Anucchūna* (~ non-elevated lesion). Irrespective of origin, site, size of patches with disease duration of 1-3 year and willing to participate and give written consent were included in the study. Aapparently healthy individuals aged (18-60 years) with no history of any skin disease, systematic or infective disease for the past six months were taken as control.

Patient with history of burn and trauma, non-cooperative and patient on immunosuppressive therapy, pregnant and lactating women or with a history of diabetes mellitus, hypertension hyperthyroidism or any other systematic and infective disease were not included.

Assessment of exposure status and other variables

The exposure status was assessed through validated case record format through one-to-one interview after due written informed consent taken.

All the patients were interviewed and asked for demographic and clinical details like age, sex, family history, age of onset, site of onset, duration of disease, past treatment, marital status, dietary habits, precipitating factors and associated disorders through a simple and validated questionnaire with different modality converted into simple and easy questions. Total 93 questions were asked from participants. Participant were assessed on 5-point LIKERT SCALE, with options of never (0), rarely (1), sometimes (2), often (3) and always (4). Thus Cumulative (total) score for *viruddha aahara* along with other etiological factors ranged from 0 to 372 based on 93 questions. For computing odds ratios, score 0 to 2 was considered as 0 (Very rarely) and 3 & 4 as 1 (often).

Initially risk assessment was done using univariate data followed by multivariate model to identify significant risk factors for each of the 15 domains and predicted probabilities were computed to use in final multivariate logistic model to assess final determinants

of *Shvitra* (Vitiligo). Analysis was done using SPSS v.26. We found 41 parameters statistically significant with p-value less than 0.05, chi-square > 3.84 and O.R. more than 1. In present article 35 questions were not shown because they had value lying in never or sometimes category.

Papakarma was assessed through 4 questions using a questionnaire validated by 10 Professors from NIA Jaipur, BHU Varanasi and AIIA Delhi. We avoided assessment of depression, anxiety and stress scales that would have different aspects and lengthy questionnaires.

Vitiligo on modern parameters was divided into 5 types: Total One or more macules in one area but not in segmental pattern were grouped as focal vitiligo; one or more lesions localized in unilateral pattern as segmental vitiligo. Macules localized on the face and distal extremities as acrofacial vitiligo; symmetrical distribution of lesions affecting many parts of the body as vitiligo vulgaris; unique involvement of mucous membrane as mucosal and depigmentation involved in more than 80% of the body as universal vitiligo.

Shvitra (vitiligo) severity scale (SSS) was taken from Ayurveda text, where assessment of disease severity was based on size, number, colour, presence of hairs and itching. SSS ranges between 0 to 25.

Prakriti assessment was done through validated performa of CCRAS with due permission.

For bio-chemical markers *i.e.,* CBC (Beckman Coulter LH- 780, Automatic 6-part haematology analyser), ESR (Wintrobe's method), Sr. Insulin and Hs-CRP (ELISA method) testing was done in the clinical pathology laboratory of the institute. Sample was separated and stored at -80-degree Celsius temperature and testing done through ELISA method after completion of enrolment of cases as well control.

Results

Demographic and clinical profile

The demographic details of both the groups are shown in Table 1. 58% of the cases were of vitiligo vulgaris, 28% of Acro facial vitiligo, 12% of focal vitiligo and 2% of segmental vitiligo. Vitiligo patches were present in maximum cases on the hands (18), neck (11), fingers (9), lips (8), shin (7), followed by other body areas. The onset age in the study cases ranged throughout the age criteria of 15 to 60 years, though the disease onset age was reported by maximum participants (26) as between 15-20 years, followed by 21-25 years (17), 51-55 years (15), and 31-35 years (9).

41 parameters of the risk factors were found statistically significant with p<0.00, chi-square > 3.84 and O.R.>1. In present article, 32 questions have not been displayed because they were answered as never or sometimes in both the categories, signifying that those practices were not relevant in the current scenario in the study population.

The details of the results regarding the etiological factor assessment for *shvitra* is presented below (Table 2-5). Also final result of the multivariate logistic regression was depicted in (Fig. 1).

This table describes the odds of *Shvitra* in a patient who is consuming *Virudha aahar*. Odds ratio: 0.48

A person consuming *viruddha aahar* gets 48% more chances of getting *Shvitra* than patients who were not taking *viruddha aahar.*

Bio-chemical markers

The results for the laboratory investigations conducted in the study is presented in (Table 6).

Table 1 — Participants (%) by Socio-demographic, Prakriti & Agni

Variables	Category	Cases (%) (n)	Controls (%) (n)
Age group (yrs.)	10-20	8.75 (7)	11.25 (9)
	21-30	36.25 (29)	38.75 (31)
	31-40	18.78 (15)	23.75 (19)
	41-50	11.25 (9)	22.5 (18)
	51-60	25 (20)	3.75 (3)
Gender	Male	55 (44)	58.75 (47)
	Female	45 (36)	41.25 (33)
Religion	Hindu	83.75 (67)	90 (72)
	Muslim	16.25 (13)	10 (8)
SES	Lower class	3.75 (3)	1.25 (1)
	Upper lower class	67.5 (54)	52.5 (42)
	Lower middle class	35 (21)	43.75 (35)
	Upper middle class	2.5 (2)	1.25 (1)
	Upper class	0	1.25 (1)
Occupation	Factory worker	17.5 (14)	5 (4)
	Students	13.75 (11)	16.25 (13)
	House-wife	13.75 (11)	12.5 (10)
	Cooking job	11.25 (9)	2.5 (2)
	IT/Corporate job	8.75 (7)	5 (4)
	Security Guard	7.5 (6)	10 (8)
	Others	27.5 (22)	48.75 (39)
Marital Status	Married	77.5 (62)	70 (56)
	Unmarried	22.5 (18)	30 (24)
Prakriti	*Vaataj-pittaj*	55 (44)	36.25 (29)
	Pittaj-kaphaj	30 (24)	35 (28)
	Kaphaj-vaataj	15 (12)	28.75 (23)
Agni	*Vishmagni*	60 (48)	27.5 (22)
	Mandaagni	30 (24)	37.5 (30)
	Samagni	10 (8)	35 (28)
Birth place	Uttar pradesh	43.75 (35)	36.25 (29)
	Bihar	27.5(22)	6.25 (5)
	Delhi	16.25 (13)	47.5 (38)
	Haryana	5.0 (4)	10.0 (8)
	Rajasthan	3.75 (3)	0
	Other states	3.75 (3)	0

Data presented in above Table 6, suggests that mean hemoglobin, mean corpuscular volume, total leucocyte count, high sensitivity C-reactive protein and serum insulin were significantly high in cases of *Shvitra* (vitiligo) than in controls.

Table 2 — Computed risk of etiological factor prevalent in the study

Parameter	Frequency in Case (% of 80)	Frequency in Controls (% in 80)	χ^2	P-Val	O.R. (95%C.I.)
VEGA DHARANA(Forced suppression of natural urges)					
Control of bowel movement	45 (56.3)	30 (37.5)	5.64	.01	1.50 (1.06-2.11)
Control of urge to pass urine	34 (42.5)	11 (13.8)	16.36	.00	3.09 (1.69-5.67)
UPAVASA (Fasting)					
Fasting	32 (40)	7 (8.8)	21.20	.00	4.57 (2.14-9.74)
PAPAKARMA					
Guilt due to any past deed	9 (11)	4 (5)	2.45	.12	2.78 (0.75-0.33)
Hurt anyone	3 (0.03)	1 (0.02)	1.07	.99	3.22 (0.12-79.23)
Occurrence of negative feelings	39 (48.9)	19 (23.8)	10.82	.00	2.05 (1.30-3.22)
Whether God loving/ believing person/ spiritual person	0	8	8.43	.00	0

Stratification of cases to observe relation between Hs-CRP, etiological factors, serum insulin and *Shvitra* severity score

An analysis of the observed factors of Hs-CRP, etiological factors (*Shvitra nidan* cumulative score), *Shvitra* severity score and serum insulin was done by stratifying the cases into the categories of normal (values within normal range) and abnormal (having raised values) on the basis of their Hs-CRP values (Table 7) and further on the basis of their serum insulin values (Table 8).

Cases with raised Hs-CRP values had statistically significant higher mean values for etiological factors cumulative score (243 vs 168.48), SSS (15.91 vs. 11.57), Hs-CRP (17.93 vs 2.05) and serum insulin (7.12 vs 3.16) as compared to controls and all are significantly high [p-value <0.05].

Discussion

This study is the first case-control investigation exploring diet-incompatibility (*viruddha ahara*) as a risk factor for vitiligo (*Shvitra*) and assessing its relationship with disease severity, measured by the *Shvitra* Severity Score (SSS). The research also examines the cumulative *viruddha ahara* score in relation to disease progression.

Demographic and *Prakriti* findings

No significant findings emerged from the demographic data. However, the majority of participants in both the case and control groups exhibited *vataj-pittaj* prakriti, followed by *kapha-pittaj*. According to Ayurvedic principles, individuals with

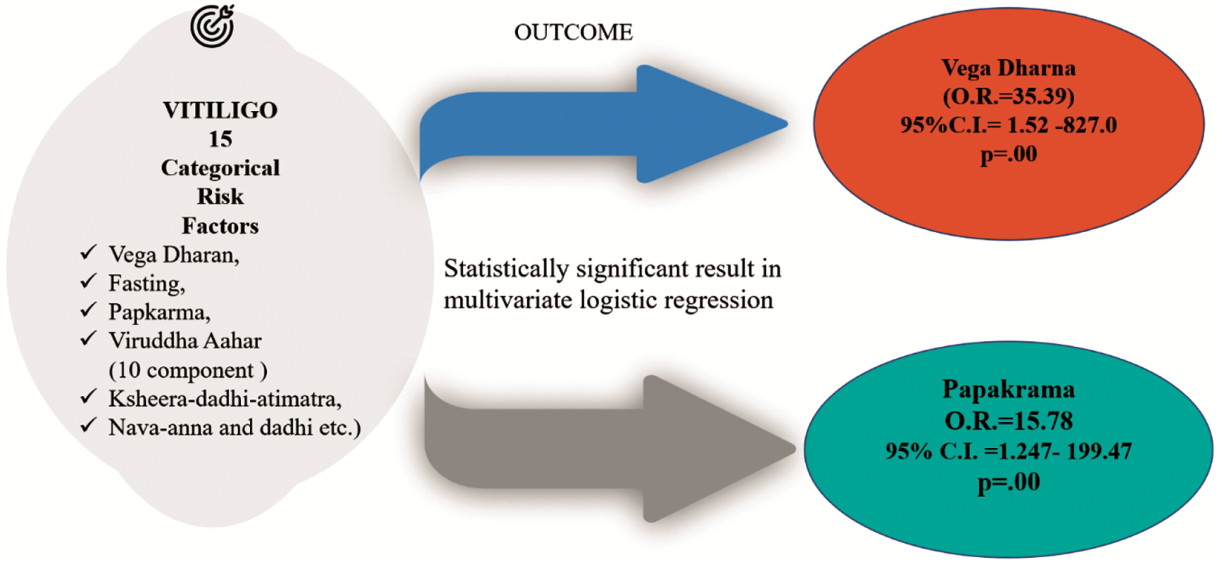

Fig. 1 — Final result of multivariate logistic regression

pitta dominance are more susceptible to *shonita dushti* (vitiated blood), which may contribute to the development of vitiligo[18]. Additionally, 60% of participants in the case group had *vishamagni* (altered metabolism), characterized by irregular digestion. This metabolic imbalance disrupts the body's physiological functions, potentially contributing to vitiligo onset[19].

Table 3 — Computed risk factors of *Viruddha aahara-vihara*

VIRUDDHA AAHARA - VIHARA					
KALA VIRUDDHA (substances which are against time or season)					
Consumption of cold items after sun exposure	32 (40)	17 (21.3)	6.62	.10	1.88 (1.14-3.10)
Consumption of cold food in summer	35 (43.8)	13 (16.3)	14.40	.00	2.69 (1.54-4.69)
Consumption of hot tea/coffee in summer season	19 (23.8)	3 (3.8)	13.49	.00	6.33 (1.95-20.5)
Consumption of spicy, sour, salty food items in summer.	34 (42.5)	16 (20)	9.42	.00	2.12 (1.28-3.52)
Consumption of roasted food in winter	40 (50)	15 (18.8)	17.31	.00	2.66 (1.60-4.42)
Excess tea, coffee or alcohol in summer	27 (33.8)	6 (7.5)	16.83	.00	4.5 (1.98-10.3)
Consuming heavy meal or food items when not feeling hungry	29 (36.3)	1 (1.3)	32.17	.00	29 (4.0-207.7)
SANSKAR VIRUDDHA (Consumption of those substances which are against mode of preparation)					
Consuming veg/non-veg dishes prepared by adding cream/ milk in it	42 (52.5)	38 (47.5)	17.33	.00	23 (1.60-4.42)
Consuming recipes cooked/mixed with honey	31 (38.8)	9 (11.3)	16.13	.00	3.44 (1.75-6.76)
VEERYA VIRUDDHA (substances which are against Potency)					
Consuming cold drink after hot food items	26 (32.5)	11 (13.8)	7.91	.00	2.36 (1.25-4.45)
Consuming egg with milk	8 (10)	0	8.421	0	0
Consuming fish with milk	22 (27.5)	0	25.50	0	0
AVASTHA VIRUDDHA, NIDRA CHA BHAJATAMA DIVA (substances which are against States or condition)					
Eating heavy food items after day sleep	29 (36.3)	5 (6.3)	21.51	.00	5.8 (2.36-14.2)
Taking curd at night	6 (7.5)	1 (0)	4.04	.12	7.25 (0.81-64.4)
Take dry, light food after physical exercise	36 (45)	3 (3.8)	36.92	.00	12 (3.85-37.3)
Exercise after consumption of heavy food item	48 (60)	9 (11.3)	41.45	.00	5.3 (2.81-10.1)
Chilled water after physical exercise	30 (37.5)	1 (1.3)	33.64	.00	30 (4.19-214.2)
Oily food after day sleep	17 (21.3)	5 (6.3)	7.58	.00	3.4 (1.32-8.77)
Taking meal just after sun exposure	37 (46.3)	0	48.13	.00	-
PARIHAR VIRUDDHA, SHEETA-USHNA-VYATYASA (substances which are against things which relieve the symptoms.)					
Tea after meal	36 (45)	8 (10)	24.57	.00	4.5 (2.23-9.06)
UPCHARA VIRUDDHA (Consumption of those substances which are against treatment)					
Drinking cold water after intake of ghee-based items	42 (52.5)	17 (21.3)	16.79	.00	2.47 (1.54-3.95)

… *Contd.*

Table 3 — Computed risk factors of *Viruddha aahara-vihara* (Contd.)

VIRUDDHA AAHARA - VIHARA					
Intake of reheated food	6 (7.5)	1 (1.7)	4.04	.04	7.25 (0.8-64.45)
Eating microwaved food	13 (16.3)	14 (17.5)	1.06	.59	0
SAMYOGA VIRUDDHA (Consumption of those substances which are against combination)					
Mango with milk	45 (58.3)	0	62.60	.00	0
Banana with milk	50 (62.5)	13 (16.3)	35.84	.00	3.84 (2.27-6.50)
Fruit salad	19 (23.8)	0	21.58	.00	N/A
Biscuit with tea	60 (75)	2 (2.5)	88.58	.00	30 (7.5-118.5)
Breakfast with tea	50 (62.5)	13 (16.3)	35.84	.00	3.84 (2.27-6.50)
Dish with curd	33 (41.3)	8 (10.0)	20.49	.00	4.12 (2.03-8.38)
Vegetables or food with milk or milk product	18 (22.5)	0	20.28	.00	N/A
Paneer (cooked or uncooked)	27 (33.8)	6 (7.5)	16.83	.00	4.5 (1.98-10.3)
Salad with meal	6 (7.5)	1 (1.7)	2.45	.12	2.78 (0.75-10.3)
SAMPAD VIRUDDHA (Consumption of those substances which are not having their proper qualities)					
Meal at in-appropriate place	23 (28.7)	18 (22.5)	.82	.36	1.27 (.75-2.17)
Consumption of previously prepared food (refrigerated or non-refrigerated)	47 (58.8)	8 (10)	42.14	.00	5.87 (2.96-11.6)
Meal at hotel	23 (28.7)	0	26.86	.00	N/A
Meal at hostel	6 (7.5)	1 (1.7)	2.45	.12	2.78 (0.75-10.3)
VIDHI VIRUDDHA (This type includes the diet which is not according with the rules of eating)					
Meals in a state of stress	18 (22.5)	11 (13.8)	2.60	.15	1.63 (.82-3.24)
Meals during indigestion	55 (68.8)	14 (17.5)	42.83	.00	3.92 (2.38-6.48)
Meal while talking or laughing	55 (68.8)	19 (23.8)	32.59	.00	2.89 (1.90-4.40)
Meal while watching television, mobile or laptop	52 (65)	17 (21.3)	31.21	.00	3.05 (1.94-4.80)
Meals after excessive hunger	42 (52.5)	17 (21.3)	16.78	.00	2.47 (1.54-3.95)

Age group and genetic factors

A significant proportion of participants in the case group were aged 15-20 years, a group more likely to consume *viruddha ahara* (incompatible food) influenced by stress, hormonal changes, and academic pressures. A genetic predisposition was suggested, with 9 out of 80 participants reporting a family history of vitiligo, pointing to potential hereditary factors.

Vitiligo subtypes and disease duration

The study found that 22.5% of participants first noticed vitiligo on their hands, followed by the neck (13.8%)[20], which is consistent with findings from other studies[1]. To minimize recall bias, only participants with a disease duration of fewer than 3 years were included, ensuring a more accurate assessment of exposure factors.

Exposure factor analysis

A study on *Shvitra* etiological factors

***Vega dharana* and metabolic disturbances**

The study found a significant association between the suppression of natural urges (*vega dharana*)[21], such as controlling bowel movement (OR:1.50, χ^2=5.65) and

suppression for urine (OR:3.09, χ^2=16.36) respectively, and the development of vitiligo. Suppressing these urges leads to the retention of waste toxins within the body, disrupting metabolic balance and promoting disease development. Constipation and improper evacuation further impair *agni* (digestive fire)[22] and gut physiology, both essential for maintaining health. This is consistent with recent research highlighting the role of gut microbiota dysbiosis in vitiligo pathogenesis[23,24].

Psychosocial factors and stress

Papakarma in this study is taken mainly as stress. Some components under the '*Papakarma*' domain could not be ascertained reliably as subjects denied any of their physical, mental, and vocal act of hurting others. Negative emotions such as stress, anxiety, and depression were found to have a high risk/exposure in vitiligo cases (OR = 2.05, $\chi2$ = 10.82, p<0.05). These psychological stressors affect the psychoneuroimmunological axis, leading to pathological changes within the body[25]. Psych dermatology is a branch that explains the effect of one's psychological status and its effect on a number of skin disease conditions like vitiligo, which is considered as a psychophysiological disorder[26]. Stress is also linked to the formation of reactive oxygen species, which damage melanocytes and contribute to the disease's development[27]. Additionally, a belief in spirituality (OR = 8.43, $\chi2$ = 8.42, p<0.05) was common among participants, often as a coping mechanism for disease management[28]. While the link between spirituality and skin conditions like vitiligo is underexplored, other studies have highlighted its role in enhancing resilience in psoriasis patients[29].future research could explore the relationships between depression, anxiety, stress, and *papa karma* in the context of vitiligo.

Table 4 — Computed risk factors of other etiological factors

KSHEERA-DADHI ATIMATRA					
Milk	38 (47.5)	14 (17.5)	16.41	.00	2.71 (1.6-4.6)
Buttermilk	36 (45)	8 (10)	24.57	.00	4.5 (2.23-9.06)
Curd	30 (37.5)	36 (45)	.92	.33	0.83 (0.57-1.2)
Other milk products	9 (11)	4 (5)	2.45	0.12	2.79 (0.75-10.3)
NAVA ANNA, DADHI, MATSYA, LAVANA, AMLA, MASHA, MOOLAKA, PISHTANNA, TILA, KSHEERA, GUDA					
Pickles	30 (37.5)	12 (15)	10.46	.00	0.4 (.22-.72)
Coffee	13 (16.3)	25 (31.3)	4.97	.02	0.52 (.28-.94)
Fish	15 (18.8)	0	16.55	.00	0
Radish	5 (6.3)	6 (7.5)	.09	.75	N/A
Excessive salty food items	11 (13.8)	0	11.81	.00	N/A
Excessive sour food items	60 (75)	11 (13.8)	60.79	.00	5.4 (3.10-9.58)

Table 5 — Final analysis using subgroup predictive probabilities

Group	No Disease	Disease	Percentage correct
No Viruddha aahaar	78	2	97.5
Viruddhha aahar	4	76	95.0
Overall percentage			96.3

Table 6 — The results for the laboratory investigations

S.NO.	MEAN (SD)		p-Value	Mean Difference	95% OF C.I.
	CASE	CONTROL			
HB (mg/dL)	13.05 (2.31)	12.24 (1.87)	.01	0.80	0.15-1.46
MCH (pgs)	29.21 (3.90)	27.16 (3.40)	.00	2.05	0.91 - 3.20
TLC (10^3/cu mm)	7.20 (2.11)	6.54 (1.59)	.02	0.65	0.07 - 1.24
Hs-CRP (mg/l)	14.65 (9.73)	4.95 (6.72)	.00	9.70	7.08 - 12.31
Serum Insulin (µIU/mL)	7.98 (12.18)	2.19 (1.93)	.00	5.79	3.07 - 8.52

Table 7 — Relation between Hs-CRP, etiological factors, *Shvitra* severity score and Hs-CRP in cases

Hs-CRP	Mean (SD)			
	Shvitra severity score (SSS)	Etiological factors (*Shvitra nidan* cumulative score)	Hs-CRP mg/L	Sr-Insulin µIU/mL
Normal (<5 mg/l) (n=21/80)	11.57 (4.19)	168.48 (11.38)	2.05 (1.47)	3.16 (5.3)
Abnormal (>5) (n=59/80)	15.91 (4.64)	243 (27.00)	17.93 (7.70)	7.12 (11.66)
p-value	.00	.00	.00	.00

Table 8 — Showing relation between serum insulin, S*hvitra* severity score, etiological factors, and Hs-CRP in cases

Serum Insulin (µIU/mL)	Mean (SD)			
	Sr-Insulin	*Shvitra* severity score	Etiological factor	Hs-CRP
Normal (<9) (n=67/80)	2.88 (1.92)	14.27 (4.97)	219.43 (41.04)	9.15 (9.46)
Abnormal (>10) (n=13/80)	30.04 (18.30)	16.69 (4.19)	233.23 (42.61)	17.13 (9.00)
p-Value	.00	.10	.27	.00

Stratification of cases on the basis of serum insulin showed statistically significant results for the mean values of Hs-CRP (p-value < 0.05) only.

Dietary factors and *Viruddha ahara*

Significant results were obtained for consumption of excessive salt, sour food items, pickles, and fish. Non-vegetarian diets are high protein foods requiring different types of enzymes to break them down. Viruddha ahara like *agni viruddha, kala viruddha, avastha viruddha, vidhi viruddha, parihaar viruddha, upachar viruddha* hamper the digestive and metabolic cascade and produce *Ama* within the body. *Hitkar* (beneficial) food is to be used by an individual, as per the digestive capacity, following the rules of eating food, as per the disease or healthy state, keeping in mind the *kala* (season), *vaya* (age), *prakriti*, *satmya*, *koshtha*, *desha* etc.[30], because the health or disease state of the individual depends on the food[31] and on the state of the *Agni*. Impaired digestion and metabolism are described as the root cause of all diseases[32], including skin disease as vitiligo. Ama, an intermediary toxic and reactive metabolite produced as a result of impaired digestion and metabolism process is crucial towards the disease pathogenetic process. This ama is highly reactive and cloggy in nature, due to which it impairs the whole gut as well as system physiology[33]. *Sampad viruddha ahara* produce the pathology due to the deficiency of proper nutrients to nourish the *rasa, raktadi dhatus* and could be possibly producing *khavaigunya* (impairment in properties of body tissues) apart from hampering of *agni* and ama production as described above. The food items which are *samyoga viruddha, samskara viruddha, veerya viruddha,* when taken together produce some new untoward properties or products within the body, which are deleterious to the body, acting like *Dushi Visha*, (slow poison)[34], causing *Rasa, Rakta, Mansa, Lasika Dhatu Dushti* in the body which further leads to development of *Shvitra* in the due course of time. Because of their synergistic action like fish with curd turns to be too cloggy for the circulatory channels because of their *abhishyandi* property[35]. Serum insulin was chosen as a biomarker in the study to indicate on the status of metabolic derangement which is an important component of disease pathogenesis as per Ayurveda.

Pathogenetic mechanisms

The study suggests that *viruddha ahara* leads to dosha and *rakta dhatu* vitiation, central to the pathogenesis of skin diseases like vitiligo[36]. A review article elaborates on the possible mechanisms in which the viruddha ahara acts and can be referred[37]. This process contributes to systemic inflammation and molecular changes, which may trigger or exacerbate the condition. Incompatible diets cause dysfunction at the tissue level, disrupting the normal flow of nutrients and contributing to *srotorodha* (obstruction in bodily channels), further aggravating the disease.

Biomarkers and metabolic disturbance

CBC and ESR were within normal range for participant in case and control groups. Highly sensitive C-reactive protein (Hs-CRP) is a quantitative test that analyses very low amounts of CRP in the serum and indicates inflammatory changes. Raised Hs-CRP in vitiligo cases has also been reported in other previous studies also[16,17]. Hs-CRP was found to be significantly higher in the case than in control groups (14.65 and 4.95, respectively) and was raised above the normal limits in 73.75% of the cases with a raised mean value of 17.93 mg/L units. Mean values of serum insulin in cases and control group were 7.98 and 2.19 respectively, although both remained within normal limit but statistically significant difference was observed between the groups. Serum insulin is released from beta cells of the pancreatic islets. It is an anabolic hormone (building block) of the body, which also helps in diagnosis of metabolic derangement. Metabolic disturbance is well accepted in pathogenesis of vitiligo[38,39]. The relationship between Hs-CRP with scoring of SSS & etiological factor and also serum insulin was found with statistically significant results. This gives a strong base for theory of *shvitra nidan* consumption in *shvitra.* The analysis of Prakriti was also undertaken, to study for the epi-genetic approach. This could further develop the concept of personalized medicine and enter the realm of personalized medicine or preventive medicine[40].

Conclusion

This case-control analytical study suggests that *vega-dharana* and *Papakarma* are the major determinants of *Shvitra* with other etiological factors also found to be significantly higher in cases as compared to controls. However, *agni, satmya* and *vyayama* status may be confounder in present study. Cumulative score of all *nidana* exhibited strong association between SSS showing habit of *shvitra nidan* consumption had greater risk of development of disease. Aetiopathogenesis, clinical outcomes of vitiligo can be correlated and understood on the basis of ayurveda-pathophysiology. Prospective

study with a larger sample size could further validate the results of this study to be applied in the population as preventive and treatment modules.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Author Contributions

PM-Conceptualization; Formal analysis; Investigation; Methodology, Analysis, Writing - original draft. AM- Conceptualization; Supervision; Editing Original draft. AK- Data analysis, Data curation. SR- Conceptualization; Supervision; Editing Original draft. GPR-Addressing reviewer comments, Writing- original draft.

Ethics Approval

This study was conducted after Institutional Ethics Committee (IEC) approval (IEC-AIIA/2020-PG-189) and Clinical Trials Registry – India (CTRI) (CTRI/2021/02/030941). The present article was formed in accordance with STROBE CASE-CONTRoL guidelines.

Informed Consent

Informed consent was taken from all the participants. The authors certify that they have obtained all appropriate patient consent forms and that due efforts have been made to conceal their identity for publication of results.

Data Availability

Data will be made available on request.

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