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INTEGRATED STUDY OF BIOMARKER IN *AMAVATA* W.S.R. TO RHEUMATOID ARTHRITIS

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ABSTRACT

Biomarkers are important for guiding the clinical and therapeutic management of all phases of rheumatoid arthritis because they can help to predict disease development in subjects at risk, improve diagnosis by closing the serological gap, provide prognostic information that is useful for making therapeutic choices and assessing treatment responses and outcomes, and allow disease activity and progression to be monitored. Rheumatoid arthritis (RA) is an autoimmune disease, symmetrically affecting the small joints. Biomarkers are tools that can be used in the diagnosis and monitoring of RA. *Amavata* described in Ayurvedic classics is similar to Rheumatoid Arthritis in various means.

KEYWORDS: Biomarker, *Amavata*, Rheumatoid Arthritis.

INTRODUCTION

A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule.[1]

Rheumatoid arthritis (RA) is a chronic and common systemic inflammatory disease that results in joint deformity and functional disability when not properly managed. The early diagnosis and treatment of RA are imperative for optimal disease control, greater chances of remission, and prevention of permanent clinical and radiographic damage. RA remains a clinical diagnosis although the use and discovery of biomarkers to assist with these goals remain a focus of ongoing research.

Amavata is the most common endogenous disease which is produced due to frequently formation of *Ama* in the human body. It is the commonest among chronic inflammatory joint disease in which joints becomes swollen, painful & stiff. Due to its chronicity & complications it has taken the foremost place among the joint disease. It continues to pose challenge to the physician due to severe morbidity & crippling nature. *Amavata* described in Ayurvedic classics is similar to Rheumatoid Arthritis in various means.

AIM AND OBJECTIVE

1. To understand the concept of biomarker in Rheumatoid Arthritis.
2. To understand the concept of biomarker in *Amavata* through Ayurvedic perspective.

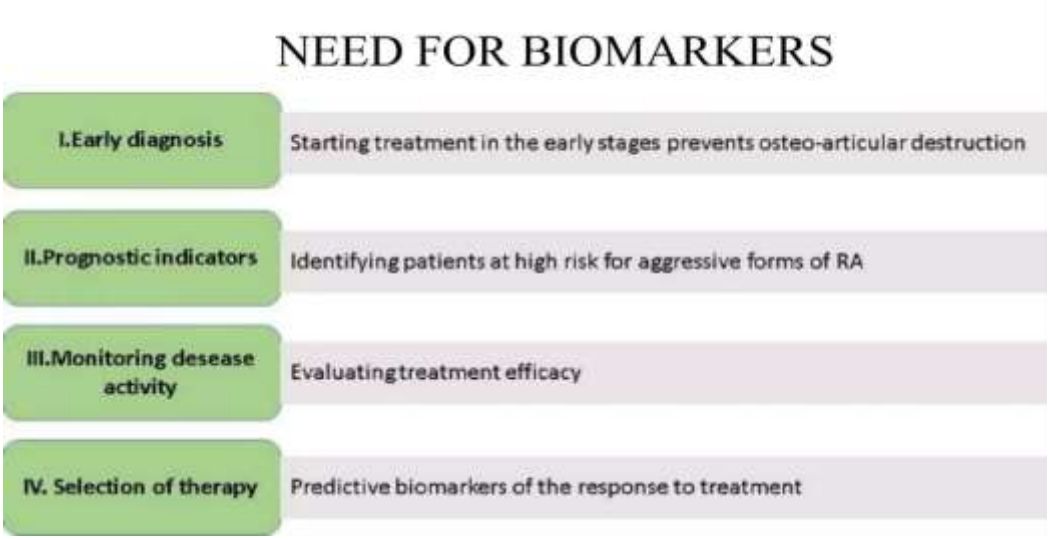
MATERIALS AND METHODS

Classical texts and modern literature is reviewed and understanding has been put forth in context to biomarkers.

REVIEW OF LITERATURE

Biomarkers in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease with autoimmune disease, joint involvement that leads to deforming and destructive arthritis of synovial joints along with multiple systemic manifestations. The aetiology of RA remains unknown, multiple mechanisms being involved in the physio pathogenic chain. So, an interest in understanding the pathogenesis of RA increased the importance of studying the biomarkers involved in different stages of the disease and diagnosis as well.



DIAGNOSTIC BIOMARKER

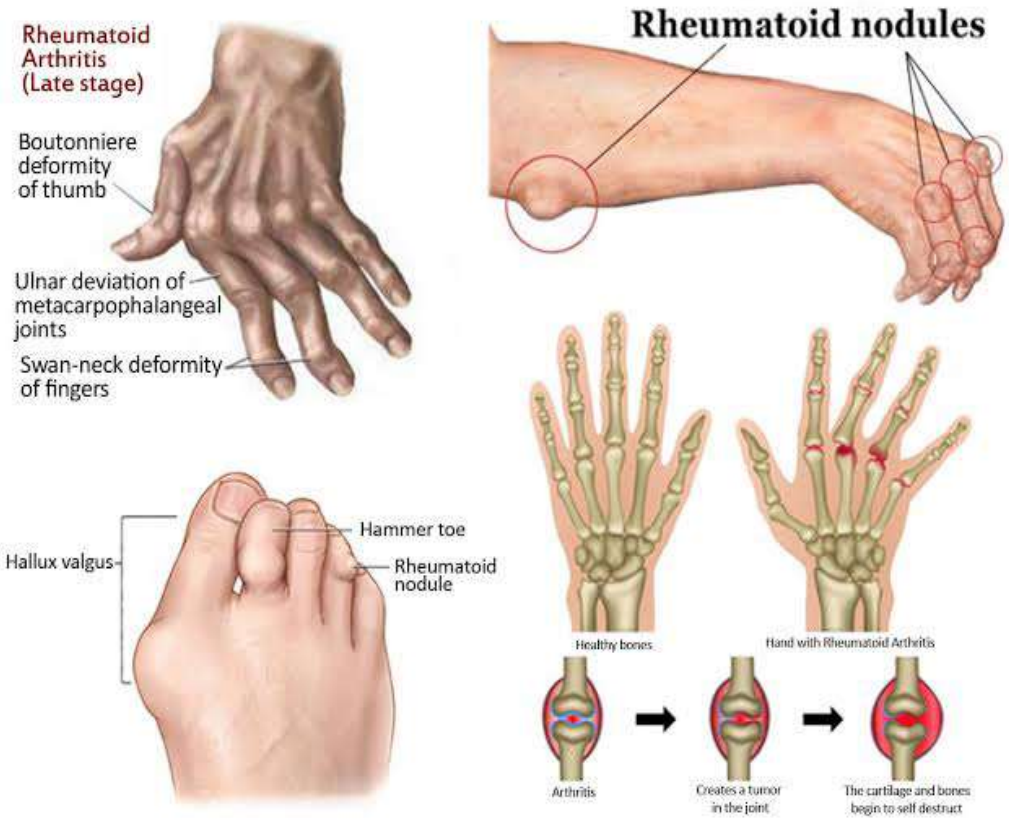
• The major role of biomarkers can be objectified by comparing the diagnostic criteria's

• The first diagnostic criteria given by American College of Rheumatology (ACR) in the year 1987 for the diagnosis of RA, which includes Rheumatoid Factor (RF) as a biomarker along with other criteria's.[2]

1987 Classification Criteria	
Criteria	1. Morning stiffness (at least one hour) 2. Arthritis in three or more joint areas 3. Arthritis of hand joints (≥1 swollen joints) 4. Symmetric arthritis 5. Rheumatoid nodules 6. Serum RF 7. Radiographic changes (erosions) on X-rays of hands
Applicable for	All arthritis patients
Results in	Classification of RA (yes/no)
Positive in case	Four of the seven criteria must be present. Criteria one through four must have been present for at least six weeks.
Test characteristics	Sensitivity of 79%–80% and specificity of 90%–93% for established RA. Sensitivity of 77%–80% and specificity of 33%–77% for early RA.

2010 ACR/EULAR Criteria for RA Diagnosis		
A.	**Joint involvement**	
	1 large joint	0
	2-10 large joints	1
	1-3 small joints	2
	4-10 small joints	3
	>10 joints (≥1 small joint)	5
B.	**Serology (≥1 test result needed)**	
	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
C.	**Acute-phase reactants (≥1 test result needed)**	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
D.	**Duration of symptoms**	
	<6 wk	0
	≥6 wk	1
	Definite diagnosis requires total score ≥6/10.	

Affected Joints



Biomarkers in RA

• Autoantibodies

- Rheumatoid factor (RF).
- Anti-citrullinated peptide antibodies (ACPA)

• Acute-phase reactants

- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)

• Newer biomarkers

- MBDA
- 14-3-3-eta

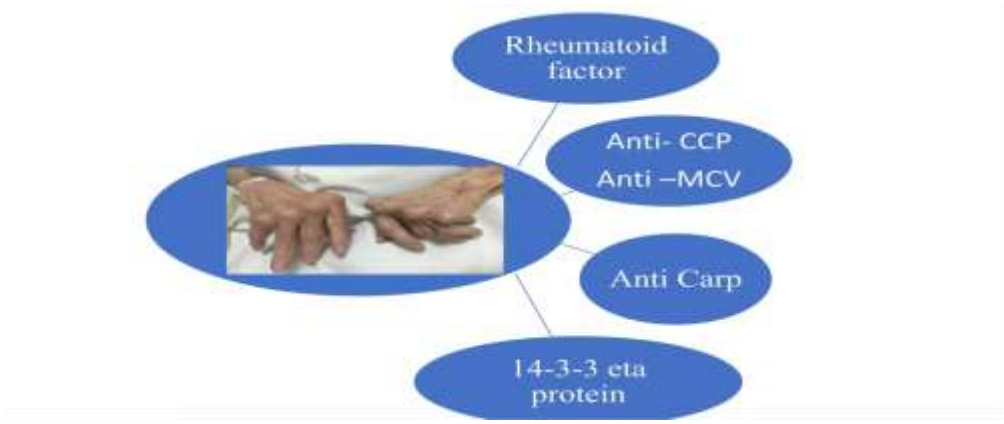


Figure of biomarkers in RA.

1] RHEUMATOID FACTOR

•Rheumatoid factors(RFs) are polyreactive ÎgM antibodies produced by a subset of B Lymphoctes and bind to the Fc portion of the IgG molecule.

Sensitivity :60 to 80% for RA

Specificity :80 to 95%.

The normal range of RF is from O-20 IU/mI

RF above 20 IU/ml is not considered enough to diagnose RA Other autoimmune diseases conditions, chronic infections, diabetes, bacterial endocarditis, cancer, normal aging may express RF.

2] ACPA - Anti-citrullinated peptide antibodies

Anti-citrullinated protein antibodies (ACPAs) are autoantibodies against citrullinated peptides and proteins. The specificity of anti-cyclic citrullinated peptides (anti-CCP), which belong to ACPAs, is 88–98%. Therefore, ACPAs may be reliable markers for the early diagnosis of RA.

Anticyclic citrullinated peptide (anti-CCP)- This test is 97% specific for RA if it is present.

The normal level of anti-CCP is less than 20 Units by different measurement notation, that is, as less than 20 EU/ml.

* RF and anti-CCP are not used to monitor disease activity, because they both tend to remain positive despite remission.

3] SEDIMENTATION RATE

Erythrocyte sedimentation rate or ESR is a simple measure of inflammation

It is calculated by measuring the rate at which red blood cells sediment in a test tube in one hour

•Normal levels for men: 0-15 mm/hr to 0-20mm/hr

women :0-20 mm/hr/ to 0-30mm/hr

The ESR is not specific for RA, such as bad processing, infection, and aging in patients over the age of 50

4] CRP: C-Reactive Protein is routinely assessed as a marker of systemic inflammation in RA. However it is also an immune regulator that plays an important role in inflammatory pathways associated RA and promotes atherogenic effects.

5] Anti-MCV - MUTATED CITRULLINATED VIMENTIN ANTIBODIES[3]

Anti-MCV are used as efficient biomarkers for estimating progress of RA. Main advantage of testing for anti-MCV is the early appearance of the anti-MCV antibodies, what allows for detection of early RA and submits adequate therapy just after the disease's onset.

6] ANTIBODIES AGAINST CARBAMYLATED PROTEINS (ANTI-CARP)

• Anti-carbamylated protein antibodies (anti-CarP) are reported to be associated with increased disease activity and with more severe joint damage in RA patients.

7] 14-3-3 ETA (n) PROTEIN[4]

- 14-3-3 eta protein belongs to the family of 14-3-3 proteins that consists of 7 isoforms, it is located intracellularly, being externalized in the inflammatory process where it can be citrullinated
- This is the newest blood test to be used in the diagnosis of RA. People with RA seem to have elevated levels of the 14-3-3 protein in their blood, the 14-3-3 test may be used with other lab tests in the early diagnosis of RA

The value of 14-3-3" more then >0.19 ng/ml

OTHER BIOMARKERS[5]

- Cartilage oligomeric matrix protein (COMP) is a specific serological marker, evaluates the articular cartilage degradation and its turnover, its detectable in the blood and synovial fluid
- Serum calprotectin is a protein that has the ability to bind calcium, belonging especially to leukocytes, but can also be found in monocytes or macrophages. High levels of calprotectin can appear in various inflammatory conditions
- Survivin, a tumoral biomarker, which belongs to the family of inhibitors of apoptosis, has been reported in patients with RA

Biomarker	Presence(P)/Absence(A)	Predictive role
FR,Anti-CCP	Neither P or A	-
FR,Anti-CCP	P	++
Anti-MCV	Neither P or A	-
Anti-MCV	P	+
14-3-3eta	A or low levels	+
COMP	A or low levels	+
Calprotectin	P	+
Survivin	A or low levels	+

Biomarkers in Amavata

Anything that can be used as an indicator of a particular disease state can be considered as biomarker. Progression of disease depends upon *Samprapti* that includes *Nidana, Purvarupa, Rupa, Upasaya-Anupasaya, Samprapti, Upadrava, Sadhya-Asadhyata, Arishta Lakshanas.* Thus, in *Ayurveda* all these features may be regarded as Biomarkers.[6]

Amavata is the outcome of *Agnidushti*, *Amotpatti* and *Sandhivikruti*.

1. "*Amena sahita vata Amavata"*.[7] The virulent *Ama* circulates in the whole body propelled by the vitiated *Vata Doshas* producing blockage in the body channels that stations itself in the sandhi giving rise to *Amavata*.
2. The combination of *Ama* & *Vata* form *Amavata*, it shows the predominance of *Ama* & *Vata* in the *Samprapti* of *Amavata*.
3. *Ajeerna* produce *Ama* & along with *Vata* it produce *Amavata*.

The condition in which Vitiated *Ama* and *Vata* simultaneously lodge in *Trika* and *Sandhi*(Joints) leading to *Stabdhata*(Stiffness) of the body is known as *Amavata*.

Diagnostic Biomarkers

Diagnostic biomarkers define a population with a specific disease. It may be simulated with *Lakshanas* of disease.

Pratyatma Lkshana* of *Amavata

1. *Sandhi Shotha* - Swelling in multiple joints
2. *Sandhi Shoola* - Pain in the joints
3. *Gatra Stabdhata* - Stiffness in the body

Pratyama Lakshana	**Samanya Lakshana**	***Pravrudha Lakshana***	***Doshanubandh Vaat***	***Doshanubandh Pitta***	***Doshanubandh Kapha***
Sandhishool	*Angamarda*	*Vrushchik Danshavat Vedana*	*Shool*	*Daah*	*Staimitya*
Sandhishoth	*Aruchi*	*Agnidaurbalya*		*Raga*	*Guruta*
Stabdhata	*Trushna*	*Prasek*			*Kandu*
Sparshasahtva	*Alasya*	*Nidra Viparyay*			
Sanchari Vedana	*Guarav*	*Vairasya*			
	Apaak	*Daah*			
	Jwara	*Bahumutrata*			
	Shunta Anganam	*Antrakujan*			

Nadi Pariksha: 'According to *YOGA RATNAKARA* all the diseases can be diagnosed from *Nadi* and it was compared with strings of *Veena* playing all the ragas which signify the importance of *Nadi Pariksha*.' This is a very special type of noninvasive diagnostic technique where by the use of three fingertips only and pulse of the patient a diagnosis can be achieved

within no time. This can provide the information about the exact location and nature of the disease.

Nadi Gati we found in *Ama* condition is *Gurvi* i.e. heavy and *Gariyasi* i.e. tense in nature.

Mala Pariksha: *Jala Nimajjana Purisha Pariksha* is also another tool through which the status of *Agni* and the presence of *Ama* can be detected.
If *Mala* sinks in water, it indicates the presence of *Ama*. If it floats, then *Ama* is absent in *Mala*.

Mutra Pariksha
Vanga Sena: Author specially mentioned that "*Takra Tulya Mutra*" as *Lakshana* in *Amavata*.[8]
Vasavarajiya: In this text author has specially explained the "*Pitamutrata*" as *Lakshana* of *Amavata*.
Madhavnidana: Vivrudha Lakshana of *Amavata – Bahumutrata.*

Jivha Pariksha
Jivha Pariksha is mentioned by *Acharya Yogratnakar* under *Ashtavidha pariksha*.

Jivha Pariksha reveals our main constitution (normal *Prakruti*)°, imbalance of *Doshaja*, state of *Agni* (digestive fire) and *Koshtha* (*Annavaha Strotas*).According to *Ayurveda Agnimandya* (hypo functioning of digestive fire) is the root cause of all diseases. The state of the *Agni* is thus assessed by the condition of the tongue. Thick coating points to the progression of disease. So *Jivha Pariksha* has diagnostic and prognostic values as well.

Saam jivha (Coated) indicates a presence of *Ama* (undigested food) in the digestive system.

Production of *Ama* (toxins) in the body is the cause of coated tongue which is found in the *Amavata* patients.

Coating in middle part of the tongue indicates the presence of *Ama* (toxins) in the stomach and in the small intestine.

Coating in posterior part of the tongue indicates presence of *Ama* (toxins) in the large intestine.[8]

Upashayanupshaya

Upashaya is not treatment, but more of a trial to confirm the diagnosis prior to treatment by the application of drug, food or regimen.*Amavata Lakshanas* such as *Sandhishotha, Sandhishool* etc are likely to be found in other diseases like *Vatarakta, Sandhigatvaat, Kroshtukshirsha* etc. In this difficult condition *Upashaya* and *Anupshaya* have advised.

Upashaya for *Amavata* are *Ruksha Sweda, Snehavarjit Sweda, Langhana, Ushnakala* etc.

Anupashaya: By boosting *Amavriddhi, Santarpana* worsens the disease's state, and *Snigdhata* causes *Srotoabhishyanda*. Due to *Sheeta* and *Kleda Vriddhi*, they also regard oiling, overcast weather, and early hours to be *Anupashaya* for *Amavata*. Because of this, the *Samavastha* of *Amavata* uses the use of oil as a diagnostic method.[10]

DISCUSSION

Normal interactions between *Doshas* and *Dhatus* are essential for maintaining good health. Accordingly, individuals with abnormal *Doshas* and *Dhatus* are more vulnerable to pathognomic conditions. It also weakens the *Agni* that decreased immune surveillance. Alteration in these bodily components results in disease manifestation and these conditions can be indicated well by biomarkers. Sustained and collaborative efforts between *Ayurvedic* physicians and clinicians regarding unexplored concept of biomarkers may lead to a deeper understanding of certain modern and traditional principles. Understanding to various biomarkers in Rheumatoid Arthritis and *Amavata* has been discussed through *Ayurvedic* and modern perspectives.

Biomarkers of Immunotoxicity

Interplay between diet and host regulates *Agni*. Digestion of food depends on *Prakriti*, status of *Doshas, Agni* and digestive factors. *Aam* at acute, sub-acute or chronic conditions appears to relate to the gastro-intestinal as well as metabolic disturbances engendered due to impairment of *Antaragni*. This affects *Ojas* and *Vyadhikshamatva* of person and may affect immune system

Inflammatory biomarkers

Ama on having interaction with *Dusta Dosha* and *Dhatus* causes *Srotorodha* and is responsible for inflammation and tissue damage due to change in their biophysical properties. *Ama* circulates and interact with excretory products gets localized in micro-channels of the

body becomes toxic and forms pro-inflammatory waste product that triggers pathogenesis and hamper various physiological functions. *Ama* can be found on the tongue and in urine, thus considered to be a reliable biomarker that links abnormal digestive status with the onset of inflammation.

Biomarkers for Susceptibility

There are innumerable factors responsible for health status of person that influences susceptibility of exposed individuals. *Srotovaigunyata* reflects the area of susceptibility through acquired factors or genetic predisposition that influences response to exposure that is different in different individuals and triggers *Vyadhi Utpatti*.

On the *Dhamanies* with the other *Doshas Ama* facilitates *Sroto-Abhisyanda & Srotorodha* causing *Sthanasmsraya* manifested *Stabdhata, Sandhi-shool, Sandhishotha, Angamarda, Apaka, Jwara, Anga Gaurava, Alasya* etc symptoms of *Amavata.*

Surrogate Biomarkers

It is intended to substitute for clinical end point. It is further expected to predict clinical benefits based on involvement of bodily components. Clinical end points may also be taken as *Upadrava* or *Arishta Lakshanas* as they predict the health status and stage of disease.

Upadrava is a sequel that follows the symptoms of the primary illness. According to *Acharya Dalhan*, symptoms that are linked to a sickness over a longer period of time are referred to as *Upadravas*. Disease either erupts and takes on a terrible form or remains persistent in nature.

The symptoms of advanced stage of *Amavata* are considered as *Upadrava* of *Amavata* disease.

Various *updravas* of *Amavata* as mentioned by *Acharyas* are tabulated as follows

Sr.No	*Acharya*	*Updrava*
1.	*Vijayrakshit*	*Khanja, Sankocha*
2.	*Harita*	*Angavaikalya*
3.	*Madhava*	*Trushana, Chardi, Bhrama, Murchha, Hridyagraha*
4.	*Vachaspati*	Various *Vatika* disorders

Prognostic Biomarkers

Prognostic biomarkers correlate with outcomes. Prognostic markers form the basis for establishing the prognosis. It may be related to *Sadhya Asadhyata* of any *Vyadhi*.

Prognostic biomarkers for *Amavata* as follows

- *Ek doshaja*/limited *hetus*/recent origin/few signs and symptoms- *Sadhya* (Can be cured)
- *Dvidoshaja*/many *hetus* and signs and symptoms/chronic- *Yapya* (Medicine is required for as long as patient is alive)
- *Sannipataja/Updravas* like *Sarvangashotha*, *Hridgraha*- *Krichhasadhya* (Difficult to cure).[11]

CONCLUSION

Thus, Biomarker is an alteration in the constituents of tissues or body fluids that are associated with the derangement in *Doshas* and *Dushyas* along with some subjective parameters that could be used as *Ayurvedic* biomarkers in various aspects. The principles of traditional systems of medicine could be developed into hypothesis and concepts should be validated in light of modern scientific methods that may lead to the development of various unexplored concepts like biomarkers in *Ayurveda*. Early diagnosis of RA continues to be a challenge. The disease needs to be distinguished from other self-limiting arthritis and connective tissue disease. Some biomarkers are not specific and some are not widely used due to technical problems and they are time consuming as well as expensive. On the other hand, As RA is correlate with *Amavata* in Ayurveda, the biomarkers considered for *Amavata* are more specific and cost effective and helps in early diagnosis of disease.

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